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UNIVERSITY OF ALBERTA

Synthesis of Cysteine Derivatives and Hydrazinoserine

BY

James Theodore Kapron ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

Edmonton, Alberta

Spring 1993

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled Synthesis of Cysteine Derivatives and Hydrazinoserine submitted by James Theodore Kapron in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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E. E. Knaus

Dr. Edward E. Knaus

Paul Harrison.

Dr. Paul H. M. Harrison (External)

to Gerry

and to

Vicki and Alex Kapron.

Abstract

A series of cysteine and serine analogues was prepared as potential inhibitors of enzymes which metabolize the parent amino acids. (2*R*,3*S*)-*N*-benzenesulfonyl-β-methylcysteine (**5**), (*R*)- and (*S*)-*S*-benzyl-α-methylcysteine (**40**) and (**41**), respectively, (*R*)- and (*S*)-*S*-benzyl-α-methylcysteinylglycine *t*-butyl esters (**47**) and (**48**), respectively, *S*-*p*-methoxybenzyl-*N*-phthalimidocysteinyl-D-camphor sultam (**140**), *S*-benzyl-*N*-phthalimidocysteinyl-D-camphor sultam (**141**), and enantiomerically pure (*S*)-hydrazinoserine (**151**) were synthesized.

Enantiomerically pure (2*R*,3*S*)-2-[(benzenesulfonyl)amino]-3-isothioureidobutanoic acid (**4**) is hydrolyzed in aqueous base to give **5** in 37 % yield.

(*R*)- and (*S*)-Methyl *S*-benzyl-α-methylcysteine (**31**) and (**16**) were hydrolyzed in aqueous acid to give **40** (34 % yield) and **41** (124 % mass balance of crude), respectively, which react with phosgene and subsequently glycine *t*-butyl ester to give **47** (73 % yield) and **48** (14 % yield), respectively.

Propenoyl D-camphor sultam (**110**) and propenoyl L-camphor sultam (**146**) cyclize with *N*-aminophthalimide in the presence of lead tetraacetate to give (2*R*)-4-[2-(*N*-phthalimidoaziridinyl)carbonyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (**116**) (94 % yield, 78 % diastereomeric excess (de)) and (2*S*)-4-[2-(*N*-phthalimidoaziridinyl)carbonyl]-(7*R*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (**147**) (72 % yield, 78 % de), respectively. Compound **116** reacts with *p*-methoxybenzyl thiol and benzyl thiol in the presence of boron trifluoride etherate to give **140** (56 % yield) and **141** (80 % yield), respectively.

The potential expansion of this route to hydrazinocysteines was demonstrated by the preparation of four sets of substituted D-camphor sultam aziridines: β-methyl **127** and **126** (61 % yield, 33 % de), β-phenyl **129** and **128** (90 % yield, 80 % de), β,β-dimethyl **130** (67 % yield, ≥95 % de), and α-methyl **132** and **131** (12 % yield, 70 % de).

(*S*)-*N*-Benzylserine benzyltrimethylammonium salt (**167**) reacts with *N*-methoxy-

carbonyl-3-phenyloxaziridine (**155**) to give (2*S*)-N_α-benzyl-N_β-(methoxycarbonyl)hydrazinoserine (**168**) in 26 % yield. Hydrogenolysis using palladium chloride gives (*S*)-(N_β-methoxycarbonyl)hydrazinoserine (**169**) in 56 % yield.

Hydrolysis of benzyl (*S*)-3-benzyloxy-2-[(*t*-butyloxycarbonyl)amino]propanoate (**182**) with trifluoroacetic acid and hydrogenolysis with palladium hydroxide gives **151** in 23 % overall yield. Compound **182** is formed in a minimum ratio of 98:2 inversion:retention as determined by hydrogenolysis of **151** with platinum oxide to (*S*)-serine, derivatization with N_α-(2,4-dinitro-5-fluorophenyl)-(*S*)-alaninamide (**195**) and HPLC separation of the diastereomers (*S*,*S*)- and (*R*,*S*)-serine-2,4-dinitrophenylalaninamide (**197**) and (**198**), respectively.

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First and foremost my thanks and appreciation go to my research director, John C. Vederas. Without his guidance this document could not have been assembled in its present form. Michael Klinge and Shaun Abbott are acknowledged for assistance in the preparation of this manuscript. I thank Sunil Pansare, Evon Bolessa and Daniel Niederer for collaboration. Allan Torres acquired the BIRDTRAP spectrum, Bernard Santarsiero acquired the X-ray data and Robert MacDonald helped to interpret the same data. I thank Thomas Henkel and Lister Lam for helpful discussions and interesting ideas, Pat Lane-Bell for helpful discussions and trans-2-phenylcyclohexanol, Julie Marr, Mila Sailer, the chemistry department hockey team, and Yuko Yoshizawa. Special thanks to Christopher Lowe and to all the little people who have taped me to my desk throughout the years.

Table of Contents

INTRODUCTION 1

RESULTS AND DISCUSSION 10

- 1. β-Methylcysteine 10
- 2. α-Methylcysteine 14
- 3. Hydrazinocysteines 24
- 4. Hydrazinoserine 53
  - 4.1 Oxaziridine method 54
  - 4.2 Glycerate method 61

EXPERIMENTAL 68

REFERENCES 138

APPENDIX 148

List of Tables

Table 1....................32
Table 2....................153

List of Figures

Figure 1. Methyl α-methylcysteinate preparation........................ 14

Figure 2. Heteronuclear correlation NMR spectra for compound **97** 35

Figure 3. Partial ^{1}H NMR spectrum of **89** and Eu(HFC)$_3$............ 38

Figure 4. X-ray crystal structure of **116**.................................. 43

Figure 5. Partial ^{1}H NMR spectrum of **143**.............................. 52

Figure 6. Partial ^{1}H NMR spectrum of **143** and Eu(HFC)$_3$........... 52

Figure 7. Partial ^{1}H NMR spectrum of **143**, **144** and Eu(HFC)$_3$..... 52

Figure 8. HPLC of **197** and **198**.. 66

Figure 9. HPLC of hydrazinoserine derivatives **200** and **198**......... 67

List of Abbreviations

Ac	acetyl
Ac_2O	acetic anhydride
Ala-OCH_3	alanine methyl ester
Anal	combustion analysis
Ar	argon
Ar$\underline{C}$	aromatic carbon
Ar$\underline{H}$	aromatic proton
BIRD	bilinear rotation decoupling
Bn	benzyl
br	broad
Calcd	calculated
Cbz	benzyloxycarbonyl
CI	chemical ionization
$\underline{C}(\alpha)$	alpha carbon
$\underline{C}_q$	quaternary carbon
CSR	chiral shift reagent
Cys	cysteine
δ	chemical shift
d	doublet
de	diastereomeric excess
DP	dipeptidase
Et	ethyl
Eu(HFC)$_3$	europium (III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato
GGT	γ-glutamyl transpeptidase

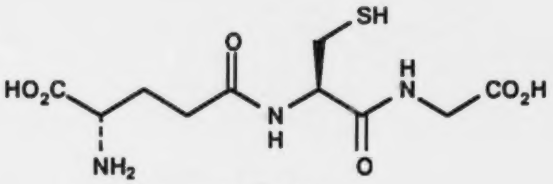
Glu	glutamate
Gly	glycine
GSH	glutathione
hetcor	heteronuclear correlation NMR spectroscopy
HPLC	high performance liquid chromatography
*i*Bu	iso-butyl
*i*Pr	*iso*-propyl
IR	infrared spectroscopy
lit	literature
LT	leukotriene
m	multiplet
MCPBA	*meta*-chloroperbenzoic acid
mp	melting point
MPLC	medium pressure liquid chromatography
oxone®	potassium peroxymonosulfate
Ph	phenyl
Pht	phthalimido
PosFAB	positive ion fast atom bombandment
ppm	parts per million
q	quartet
s	singlet
Ser	serine
t	triplet
t-Boc	*tert*-butoxycarbonyl
*t*Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran

TLC	thin layer chromatography
TMS	tetramethylsilane
TMSI	iodotrimethylsilane
t_R	retention time
triflic anhydride	trifluoromethanesulfonic anhydride
triton B	benzyltrimethylammonium hydroxide
Val	valine
X_o	D-2,10-camphor sultam

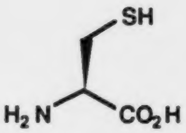
INTRODUCTION

Asthma is a worldwide and debilitating disease in which afflicted people suffer from the typical symptoms of bronchial constriction, hyperresponsiveness and excessive mucous membrane secretions. The lungs of sensitive individuals may respond to airborne antigens which stimulate an allergic response.[1] Intensive research efforts are underway to alleviate the dangerous symptoms of this disease.

Three closely related sulfidopeptides are produced in great quantities by the cells stimulated during an asthma attack.[2] These powerful anaphylaxis-inducing substances, known as leukotrienes (LTs), have been studied in great detail and their biosynthesis is well understood.[3] Each of the biologically active LTs involved in the allergic response has a key feature: the presence of a cysteine moiety in a glutathione-derived peptide portion.



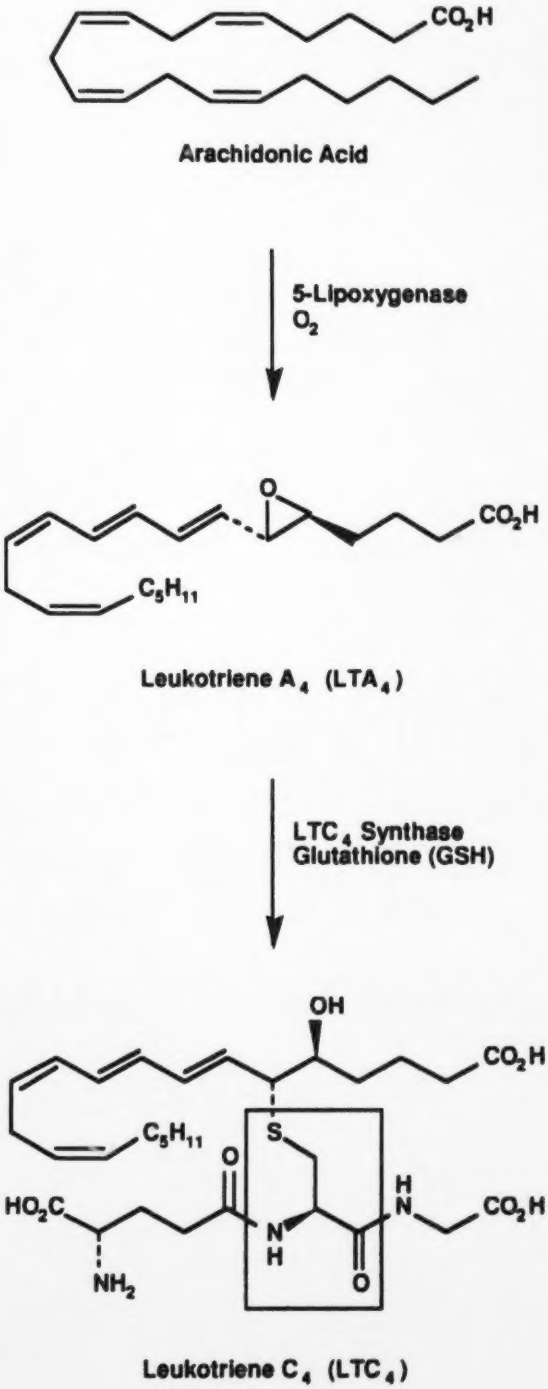
Glutathione



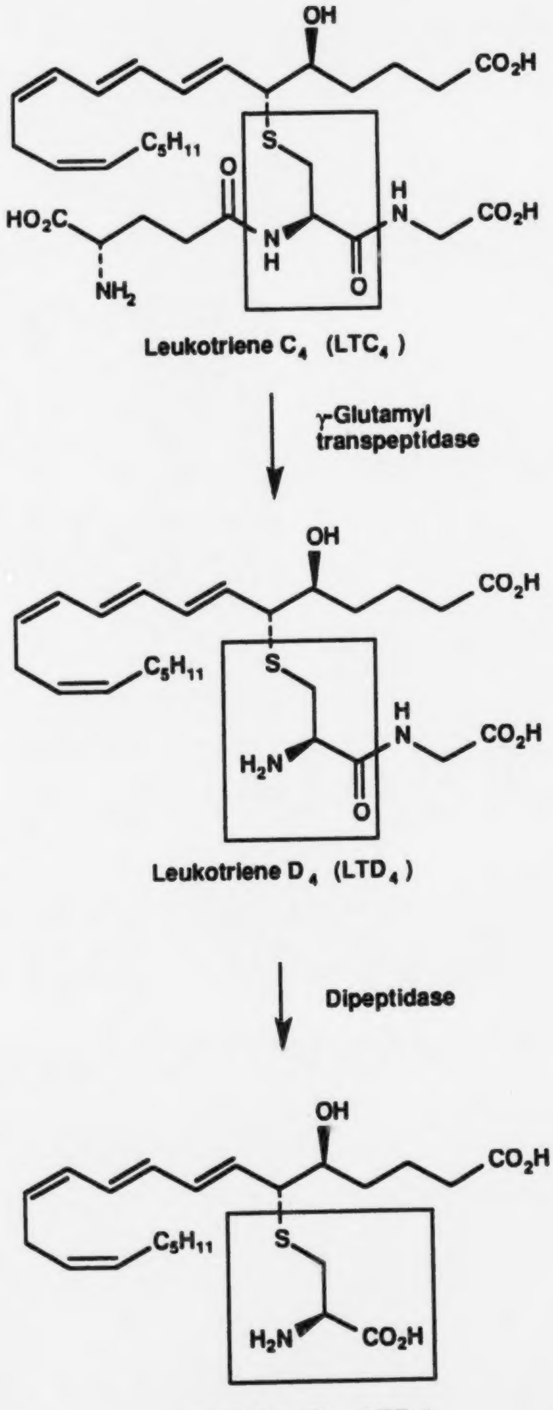
(R)-Cysteine

In the leukotriene branch of the arachidonic acid cascade, 5-lipoxygenase epoxidizes arachidonic acid at the 5,6 double bond which leads to the rearrangement of three of the double bonds to give LTA$_4$ (Scheme 1). LTA$_4$ is a precursor for many biologically active compounds, but is not one of the asthma agonists. The next enzyme, LTC$_4$ synthase, adds glutathione (γ-(*S*)-glutamyl-(*R*)-cysteinylglycine, GSH) to give the moderately active LTC$_4$. Then, γ-glutamyltranspeptidase (GGT) hydrolyses the glutamyl amide to give LTD$_4$, the most potent of the three LTs in this process.[4] LTD$_4$ contains only the (*R*)-cysteinylglycine portion in the peptide segment. An enzyme inhibitor specific for GGT may prove to be a powerful drug by reducing the amount of LTD$_4$ formed during an asthma attack.

Scheme 1
Arachidonic Acid Cascade


CO2H
Arachidonic Acid
5-Lipoxygenase
O2
O
CO2H
C5H11
Leukotriene A4 (LTA4)
LTC4 Synthase
Glutathione (GSH)
OH
CO2H
S
C5H11
O
HO2C
N
H
H
N
CO2H
NH2
O
Leukotriene C4 (LTC4)

Scheme 1
Arachidonic Acid Cascade
Continued


OH
CO₂H
C₅H₁₁
S
O
H
N
HO₂C
NH₂
H₂N

Leukotriene C_4 (LTC_4)

γ-Glutamyl transpeptidase

Most active Leukotriene

Leukotriene D_4 (LTD_4)

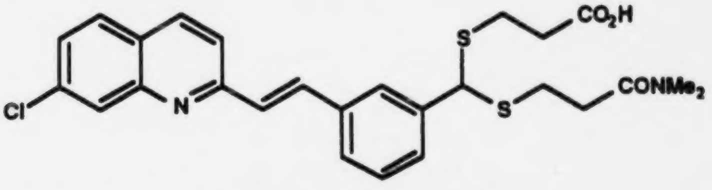
Dipeptidase

Leukotriene E_4 (LTE_4)

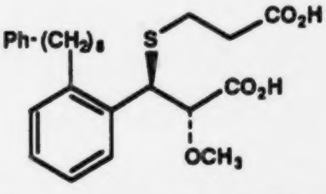
In the next step, a dipeptidase (DP) cleaves the remaining peptide bond to generate the least active leukotriene, LTE_4.[5] LTE_4 still possesses the cysteine moiety but the bronchial contracting action is severely reduced.

Interestingly, some peptides have shown biological activity when coupled to nonarachidonate derived analogues.[6] Modern asthma research seeks to find antagonists that will compete with the LTs for the active site of an enzyme or receptor involved in the biological pathway. Many receptor antagonists are currently in clinical trials to become

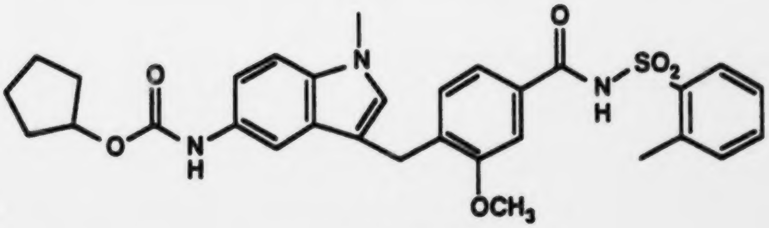
Leukotriene Antagonists



L-660,711 (Merck Frosst)



SK&F 104 353 (Smith, Kline & French)



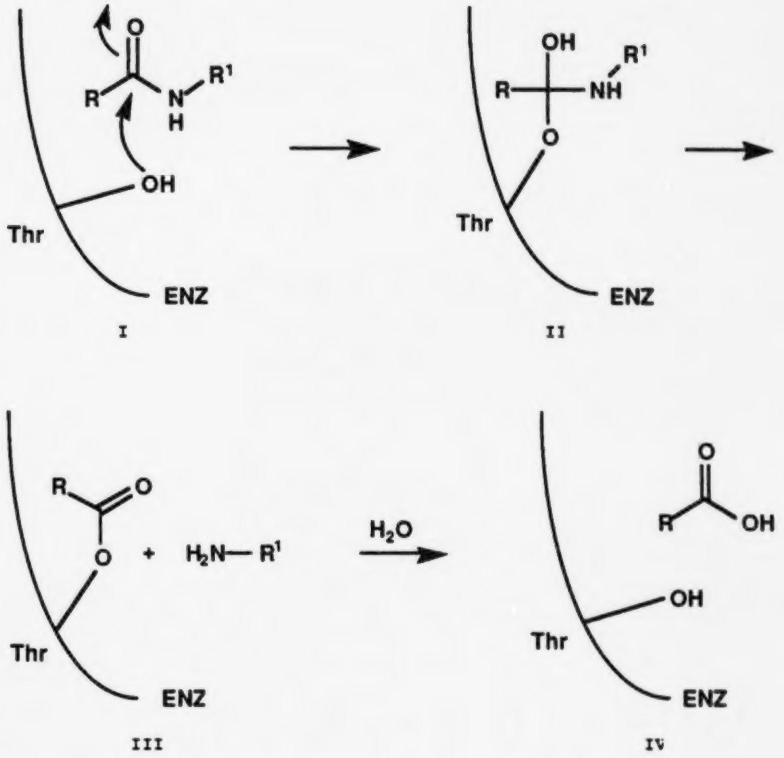
ICI-204,219 (ICI)

prescription pharmaceuticals. Among these are L-660,711 (Merck Frosst),[7] SK&F 104 353 (Smith, Kline & French)[8] and ICI-204,219 (ICI).[9] These compounds bind to the same receptor as does LTD_4 but cause no allergic response signal. Also, they prevent LTD_4 from binding and causing the dangerous symptoms of asthma. Each of these drugs lack easily hydrolyzable groups such as peptide bonds. This suggests that they can be used as orally active medications and should remain unchanged by gastrointestinal enzymes between swallowing and absorption. In contrast, any drug containing peptide bonds will not be orally active unless it has special features that reduce the rate of hydrolysis. Peptide-based drugs also have the disadvantage that they may be hydrolysed by the very enzymes that they are targeted to inhibit, thereby limiting their effectiveness.

Another potential target for asthma therapy drugs is the enzyme GGT which produces the highly active LTD_4. A highly specific GGT inhibitor should decrease the rate of LTD_4 production during an allergic shock reaction and reduce the intensity of an asthma attack. Design of a long-acting GGT inhibitor requires that the compound not be converted enzymatically into a form which does not inhibit any more.

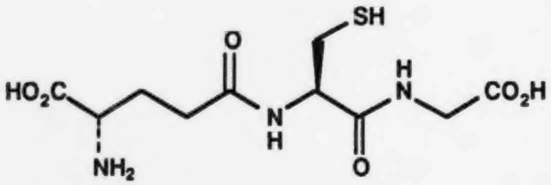
GGT has been studied extensively, and the catalytic mechanism has been described recently.[10, 11] A threonine is in the active site and this residue is involved in the formation of a tetrahedral intermediate (Scheme 2, II). The enzyme accepts many substrates provided they possess a terminal glutamyl residue. GGT will bind glutathione analogues with various substructures at the cysteinylglycine terminus.[12] For example, (*S*)-γ-glutamyl-(*S*)-2-aminobutanoylglycine is a modest inhibitor.[13] One interesting example is the GGT inhibitor acivicin.[10, 14] Acivicin possesses structural similarity to the glutamyl group and the mechanism of inhibition has been described.[15] Like receptor antagonists, enzyme

Scheme 2
Possible Mechanism of Catalysis for γ-Glutamyl transpeptidase

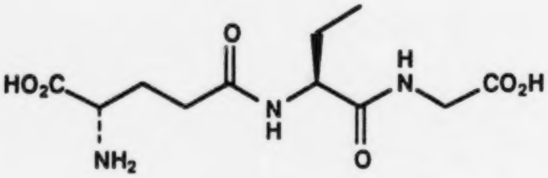


inhibitors should also be resistant to hydrolysis. Most known GGT inhibitors are peptides, thus limiting their oral activity. In addition, the sensitive triene system of LTC_4 would have to be replaced with a more robust analogue.

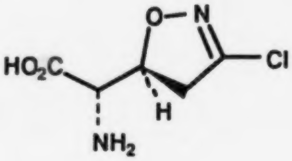
Little is known about dipeptidase, the final enzyme in LT biosynthesis.[16, 17] Renal dipeptidase is a membrane bound zinc proteinase inhibited by compounds such as cilastatin[18] and the phosphinic acid shown below.[19] An interesting use for inhibitors of pulmonary DP would be to increase the concentration of LTD_4 either in isolated biological systems or *in vivo*. DP inhibitors could also be effective biological tools for the investigation of other asthma drugs.



Glutathione

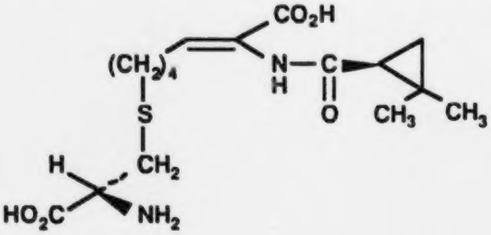


(S)-γ-Gluatmyl-(S)-2-aminobutanoylglycine

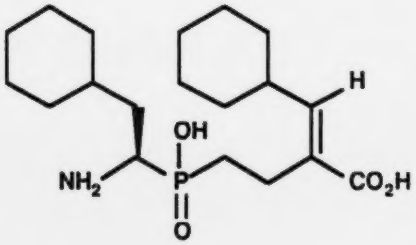


Acivicin

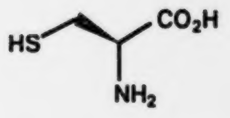
Our research aim was to synthesize novel amino acids, and peptides derived from them, which could inhibit the action of the enzymes (GGT and DP) involved in the metabolism of LTD_4. In particular, we rationalized that new substituents in place of the cysteine moiety of the LTs should hinder enzymatic hydrolysis of the natural LTC_4 and LTD_4. This research focuses on the synthesis of analogues of cysteine as well as those of serine.



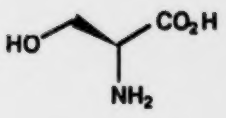
Cilastatin



(1-(R)-Amino-2-cyclohexylethyl)-3-carboxy-4-cyclohexyl-3-(E)-butenylphosphinic acid



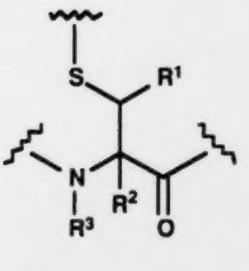
(R)-Cysteine



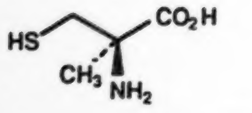
(S)-Serine

When coupled to LTA_4 or another lipophilic moiety, analogues such as α-methylcysteine, α-methylcysteinylglycine, β-methylcysteine, and hydrazinocysteine may inhibit both leukotriene receptors and the hydrolytic enzymes (GGT and DP). Since α-methyl substituted amino acids can restrict available conformations in peptides,[20, 21] their incorporation into leukotrienes should influence both binding to receptors and metabolic degradation rates. The synthesis of chiral α-methylcysteine methyl ester has been reported by Schöllkopf and Groth.[22] Many cysteines substituted at the β-postition (e.g. β-methylcysteine)[23] occur in nature.[24] Others (including β-methylcysteine)[23] have been synthesized and incorporated into peptides to restrict their conformational mobility.[21, 25-28] α-Hydrazino acids often inhibit enzymes which metabolize the corresponding α-amino acids, and peptides containing them cannot be readily hydrolysed by mammalian enzymes.[29-32] No sulfur-containing α-hydrazino acids have been reported yet.

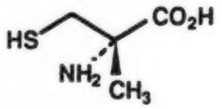
Proposed sites of substitution for amino acid synthesis



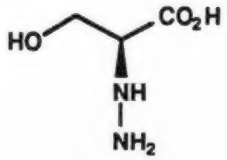
R^1 = H, CH_3
R^2 = H, CH_3
R^3 = H, NH_2



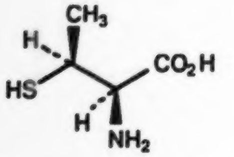
(R)-α-Methylcysteine



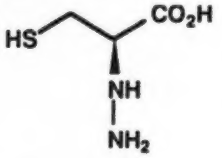
(S)-α-Methylcysteine



(S)-Hydrazinoserine



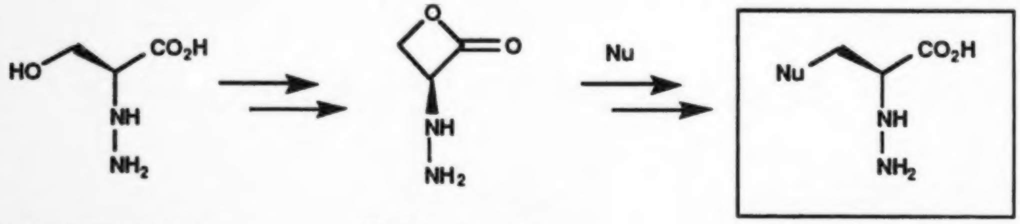
(2R,3S)-β-Methylcysteine



(R)-Hydrazinocysteine

A key target of this work was preparation of (*S*)-hydrazinoserine. This deceptively simple compound, which has never been reported, would be a useful biochemical tool because it should inhibit a host of enzymes which act on (*S*)-serine. Among the most important of these enzymes are those which require pyridoxal phosphate as a cofactor, such as serine hydroxymethyltransferase.[33] In addition, if *N*-protected hydrazinoserine β-lactone can be formed, nucleophilic ring opening at the β-position[34] would provide access to a host of biologically active chiral α-hydrazino acids, including hydrazino cysteine.

Scheme 3



(S)-Hydrazinoserine

(S)-Hydrazinoserine β-lactone

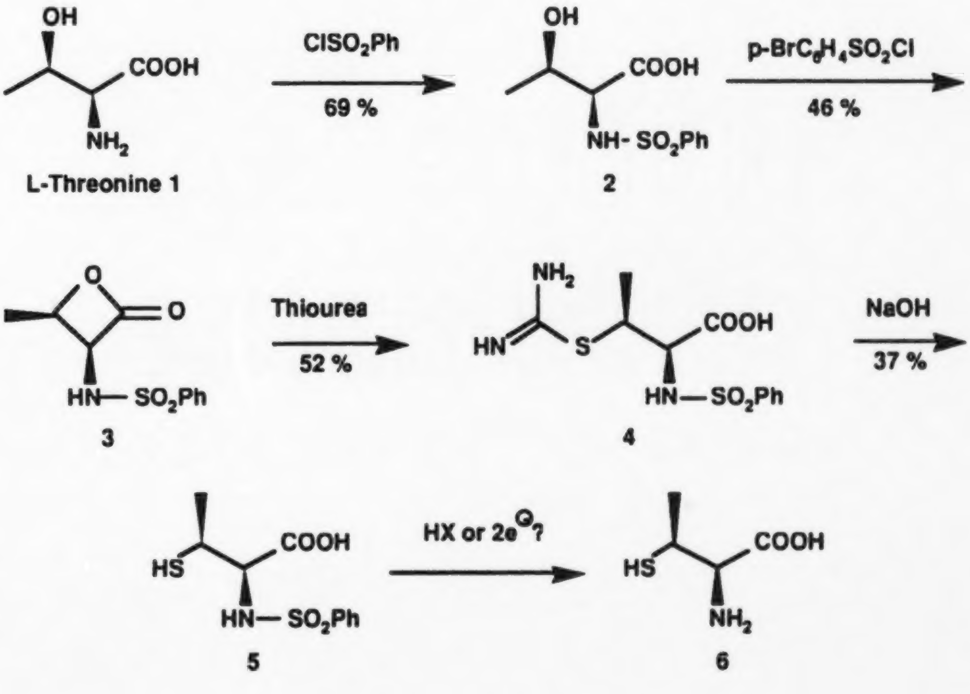
New Hydrazino Acids

RESULTS AND DISCUSSION

1. β-Methylcysteine

Assembly of the β-methylcysteine skeleton was reported by our group in 1989.[35] According to the method of Pansare, (*S*)-threonine (**1**) reacts with benzenesulfonyl chloride to give (*S*)-*N*-benzenesulfonyl threonine (**2**) in 69 % yield. Compound **2** reacts with *p*-bromobenzenesulfonyl chloride to give the (*S*)-*N*-benzenesulfonylthreonine β-lactone (**3**) in 46 % yield (Scheme 4). Thiourea attacks **3** to give (2*R*,3*S*)-2-[(phenylsulfonyl)amino]-3-isothioureidobutanoic acid (**4**) in 52 % yield (overall 16 % yield from **1**). Hydrolysis of the thiourea moiety and sulfonamide cleavage should give β-methylcysteine as the first candidate for LT coupling and biological studies.

Scheme 4

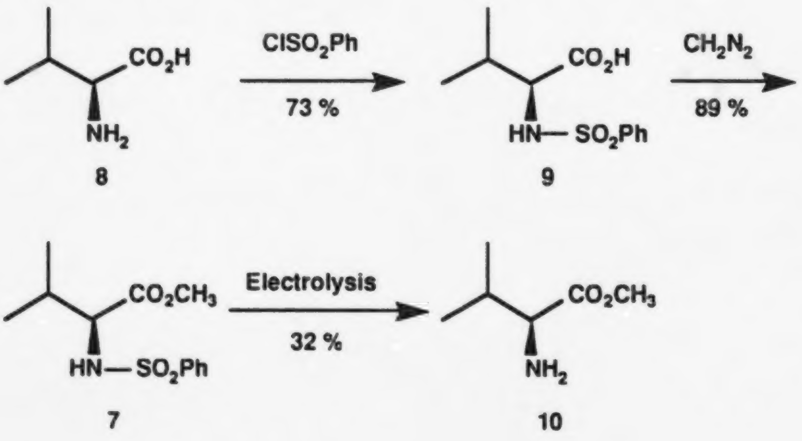

OH
COOH
NH$_2$
L-Threonine 1
ClSO$_2$Ph
69 %
OH
COOH
NH- SO$_2$Ph
2
p-BrC$_6$H$_4$SO$_2$Cl
46 %
O
O
HN— SO$_2$Ph
3
Thiourea
52 %
NH$_2$
HN
S
COOH
HN—SO$_2$Ph
4
NaOH
37 %
HS
COOH
HN— SO$_2$Ph
5
HX or 2e$^⊖$?
HS
COOH
NH$_2$
6

For the deprotection of **4**, it is important to hydrolyse to the thiol if the procedure is eventually to be used for coupling β-methylcysteine to LTA_4 analogues. The sulfonamide group must also be cleaved under mild conditions to avoid destruction of the parent amino acid. Since thiols rapidly oxidize to the disulfide in the presence of oxygen in basic solution, basic aqueous hydrolysis requires an inert atmosphere such as argon (Ar). Thus, **4** hydrolyses in 1M NaOH at 20 °C under Ar in 2 h to form (*S*)-*N*-benzenesulfonyl-β-methylcysteine (**5**) in 37 % yield.

The common procedures to remove the sulfonamide protective group are rather harsh: electrolytic reduction or refluxing 48 % HBr.[36] Hence both methods were attempted on model amino acids in order to evaluate whether either procedure would be likely to produce the required β-methylcysteine (**6**).

The first target was (*S*)-*N*-benzenesulfonylvaline methyl ester (**7**) (Scheme 5). According to the method of Maurer et. al.,[37] (*S*)-valine (**8**) reacts with benzenesulfonyl chloride in basic solution to give **9** in 73 % yield. Subsequent methylation of **9** with diazomethane gives **7** in 89 % yield. Electrolytic reduction of **7** for 2.5 h affords the expected valine methyl ester **10** in 32 % yield. Unchanged starting material **7** can also be recovered from the reaction. Since the yield was low and the reaction did not go to

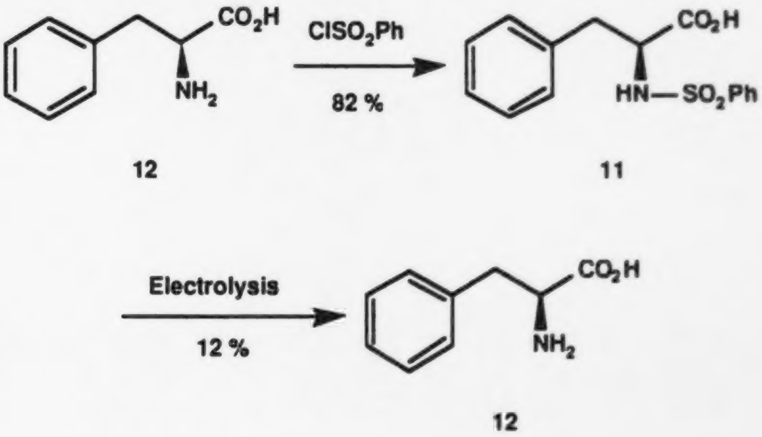
Scheme 5



completion, it appeared that a UV absorbing amino acid derivative would facilitate the detection of the reaction endpoint and perhaps lead to better yields.

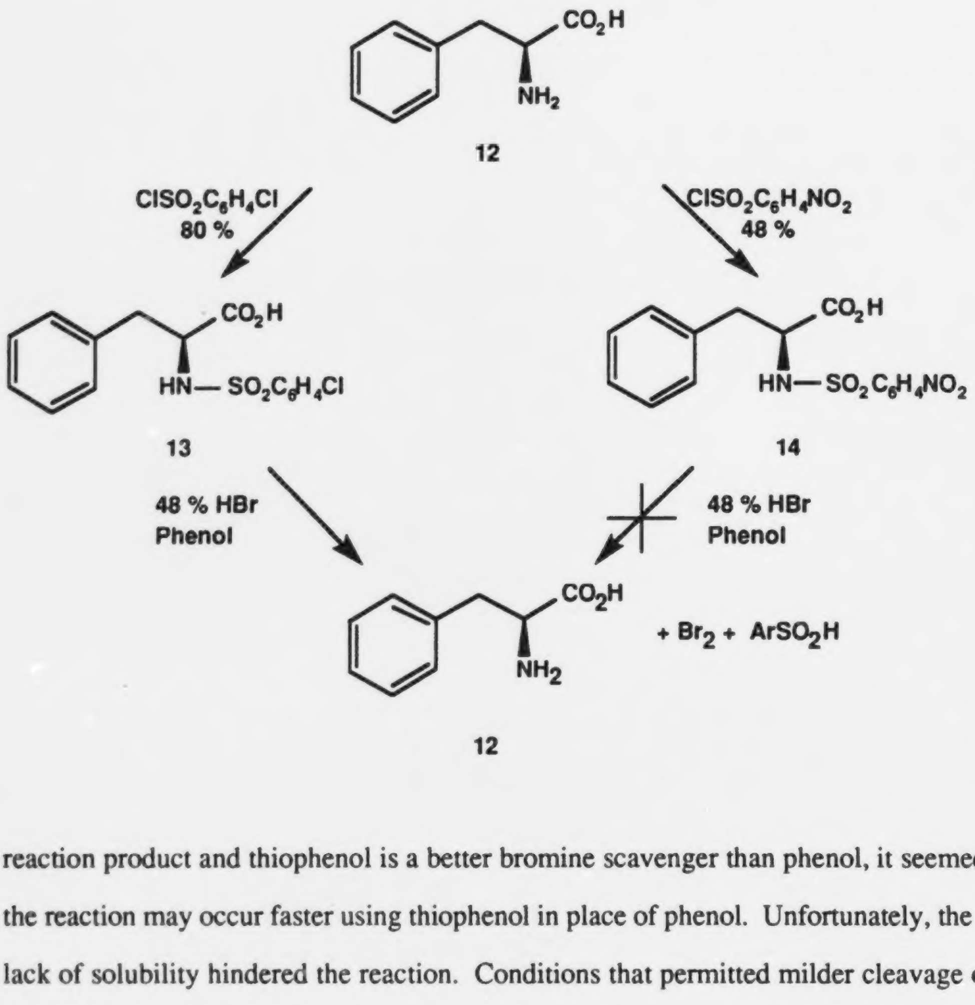
The second test compound chosen was (*S*)-*N*-benzenesulfonylphenylalanine (**11**) (Scheme 6). (*S*)-Phenylalanine (**12**) reacts with benzenesulfonyl chloride in aqueous sodium carbonate to give **11** in 82 % yield.[37] Electrolysis of **11** generates **12** after 3 h, in 12 % yield. Since derivatives **11** and **7** give poor yields, the more sensitive sulfur containing amino acids appeared unlikely to withstand this treatment.

Scheme 6



In 1952, Snyder and Heckert described a general procedure for the cleavage of sulfonamides to amines using refluxing 48 % HBr and phenol.[38] The mechanism for the reaction is not known, but products include bromine and the corresponding sulfinic acid. This hydrolysis was reexamined to determine whether the cleavage would proceed at a lower temperature. The results of these experiments are shown below. In an initial reaction, sulfonamide **11** was completely converted into phenylalanine (**12**) in refluxing HBr after 15 min. Variation of the conditions, such as using hydriodic acid or adding sodium iodide to a hydrobromic acid solution decreased the rate of reaction. The sulfonamide is not easily soluble under either of these conditions. Since bromine is a

Scheme 7
HBr hydrolyses observed by TLC


CO2H
NH2
12
ClSO2C6H4Cl
80 %
ClSO2C6H4NO2
48 %
CO2H
HN— SO2C6H4Cl
13
CO2H
HN—SO2C6H4NO2
14
48 % HBr
Phenol
48 % HBr
Phenol
CO2H
NH2
+ Br2 + ArSO2H
12

reaction product and thiophenol is a better bromine scavenger than phenol, it seemed that the reaction may occur faster using thiophenol in place of phenol. Unfortunately, the same lack of solubility hindered the reaction. Conditions that permitted milder cleavage of the benzenesulfonamide could not be found.

In order to examine whether an electron-withdrawing *para* substituent in the aromatic sulfonamide moiety could enhance cleavage under milder conditions, the corresponding *p*-chloro- and *p*-nitrosulfonamides of phenylalanine were prepared. Thus, (*S*)-*N*-(*p*-chlorobenzenesulfonyl)phenylalanine (**13**) and (*S*)-*N*-(*p*-nitrobenzenesulfonyl)-phenylalanine (**14**) were generated analogously to **11** in 80 % and 48 % yields, respectively (Scheme 7). Unfortunately the solubility of these compounds was not greater than that of **11** and only **13** cleaves to phenylalanine (**12**) in refluxing HBr/phenol.

During these investigations Roemmele and Rapoport published an exhaustive comparison of methods to cleave *N*-sulfonamide groups from protected threonines.[39] However, it remains unclear whether cysteines can be produced under these reaction conditions. In 1991, synthesis of *N*-(*o*-nitrophenylsulfinyl)threonine β-lactone was reported.[40] Unfortunately attempts to attack this compound at the β-position with sulfur nucleophiles were problematic.

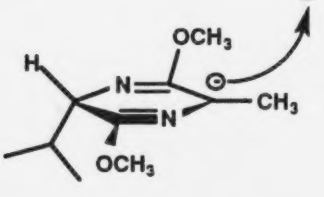
Further studies on this approach were abandoned because of the apparent difficulty of generation of a threonine β-lactone which can be converted to β-methylcysteine derivatives with a nitrogen protective group that can be easily removed.

2. α-Methylcysteine

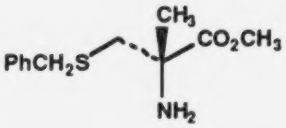
In recent years a large number of α-methyl amino acids have been prepared.[41, 42] The Schöllkopf method in particular gives high diastereoselectivity using the deprotonated valine/alanine bis-lactim ether **15** (Figure 1).[43] Electrophiles attack from the less hindered face of the ring to give alkylated products.

Schöllkopf and co-workers prepared enantiomerically pure methyl (*S*)-*S*-benzyl-α-methylcysteine **16** previously,[22] corresponding to the nonproteinogenic (*S*)-cysteine (**17**) (Figure 1). At the start of current investigations the chiral auxiliary **18** was not

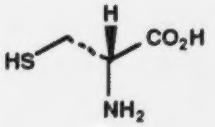
Figure 1



15



16

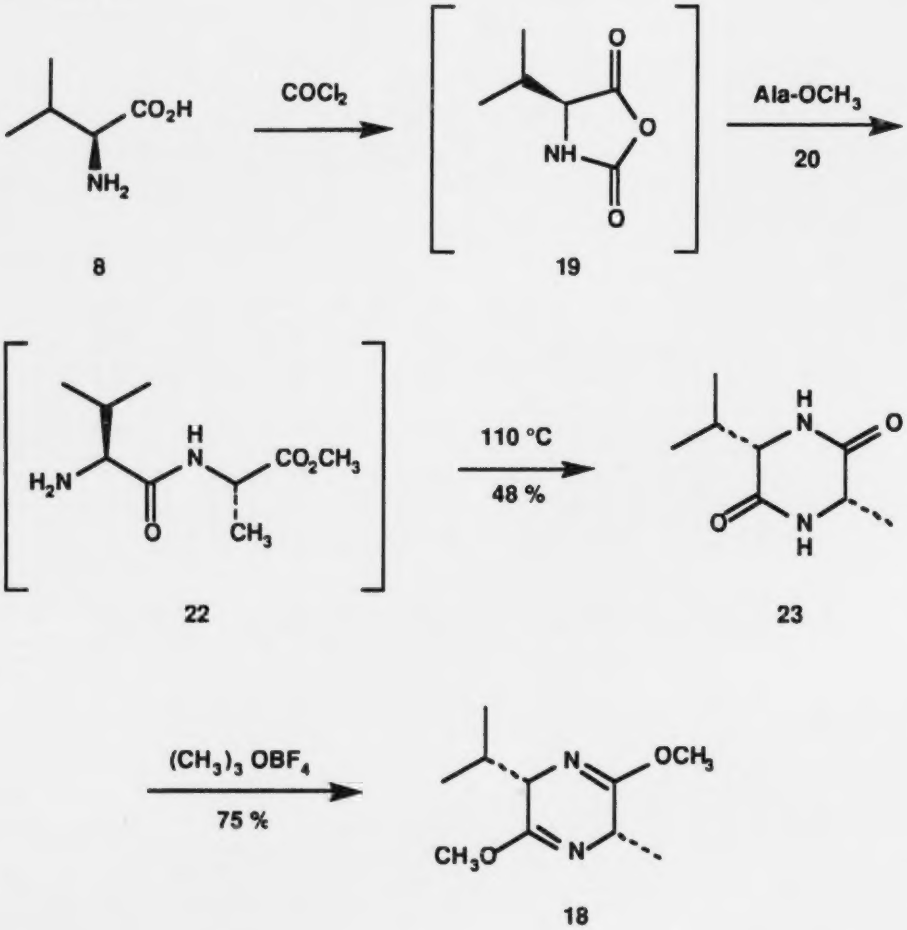


17

commercially available in Canada. Presently it is sold for over $17 per mL, which is relatively expensive for large scale preparations.

Following the literature procedure,[43] (*S*)-valine (**8**) reacts with phosgene to give the *N*-carboxyanhydride **19** (Scheme 8). This condenses with (*S*)-alanine hydrochloride methyl ester (**20**) (75 % yield from (*S*)-alanine (**21**)) in the presence of triethylamine to give the (*S*)-Val-(*S*)-Ala-OCH_3 (**22**). Compound **22** cyclizes to the diketopiperazine **23** in refluxing toluene (48 % yield from **8**). For the *O*-methylation of **23**, trimethyloxonium tetrafluoroborate (**24**) was prepared from dimethyl ether and boron trifluoride etherate

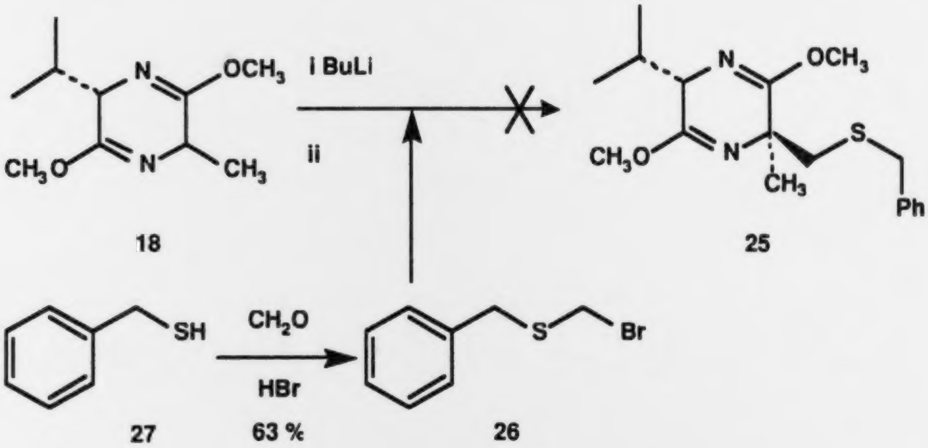
Scheme 8


CO2H
NH2
8
COCl2
O
O
NH
O
19
Ala-OCH3
20
H2N
H
N
CO2CH3
O
CH3
22
110 °C
48 %
H
N
O
O
N
H
23
(CH3)3 OBF4
75 %
N
OCH3
CH3O
N
18

in the presence of epichlorohydrin in 95 % yield.[44] The methyl Meerwein reagent **24** *O*-methylates **23** to give the bis-lactim ether **18** in 75 % yield.

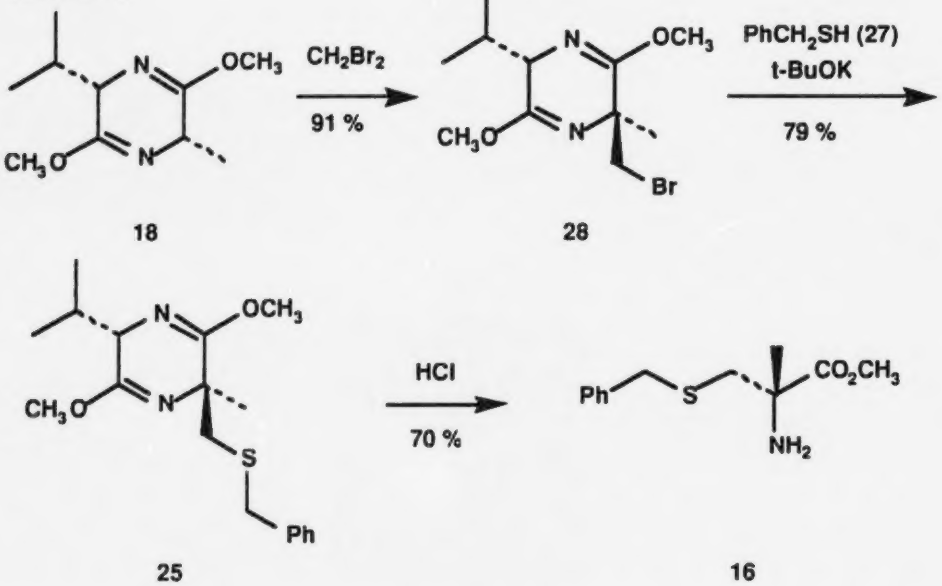
With the bis-lactim ether available, the next goal was to prepare the α-methylcysteine skeleton embedded in the pyrazine ring **25** in one step using bromomethylbenzyl sulfide (**26**) (Scheme 9). Benzyl thiol (**27**) reacts with paraformaldehyde in HBr at 50 °C in 3 h to give **26** in 63 % yield.[45, 46] However, deprotonation of **18** at -78 °C with butyl lithium and addition of **26** gave no reaction, even upon warming to 20 °C. This may be due to deprotonation of **26** followed by its decomposition.

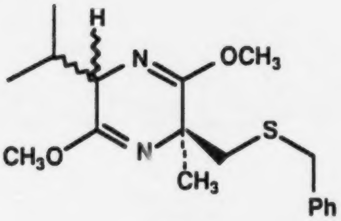
Scheme 9



Hence the literature procedure[22] for the formation of **25** was employed. The anion of **18** condenses with dibromomethane to give **28** in 91 % yield (Scheme 10). Compound **28** reacts with the thiolate anion of **27**, (formed with potassium *t*-butoxide in DMSO) at 70 °C to give **25** in 79 % yield. Interestingly, when this mixture is stirred overnight at room temperature or is heated at 75 °C, some epimerization at the carbon bearing the isopropyl group occurs to give compound **29**. This complicated the ^{1}H NMR spectrum but did not affect the stereochemical integrity of the required cysteine skeleton. Mild acid (dilute HCl) hydrolysis and separation of the amino methyl esters produces **16** in 70 % yield (overall

Scheme 10


OCH$_3$
CH$_3$O
N
CH$_2$Br$_2$
91 %
PhCH$_2$SH (27)
t-BuOK
79 %
Br
18
28
S
Ph
HCl
70 %
CO$_2$CH$_3$
NH$_2$
25
16

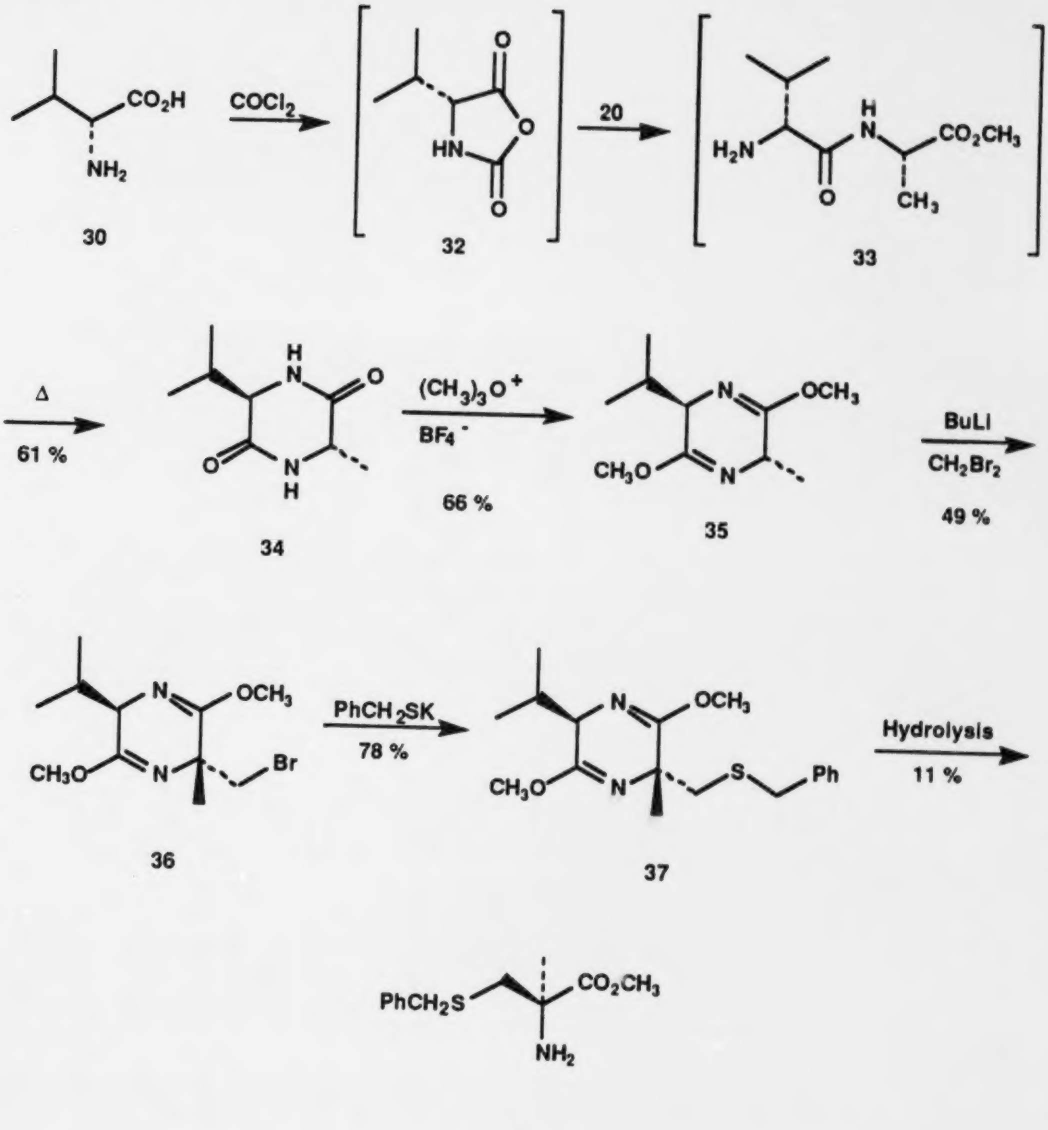

H
N
OCH$_3$
CH$_3$O
S
CH$_3$
Ph

29

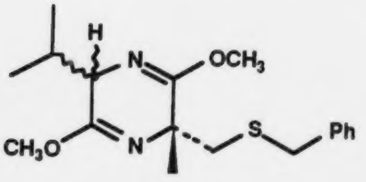
in 70 % yield (overall 50 % yield from **18**; literature yield 44 %). The isomeric series of compounds was prepared starting with (*R*)-valine **30** (Scheme 11). The α-methylcysteine methyl ester **31** (11 % overall yield) obtained *via* intermediates **32**, **33**, **34**, **35**, **36**, **37**, and **38** is an analogue of the proteinogenic (*R*)-cysteine **39**.

In order to prepare both pure enantiomers **40** and **41** of *S*-benzyl-α-methylcysteine and derivatives suitable for coupling to glycine esters, the hydrolyses of **31** and **37** were examined. Hydrolysis of the methyl ester **31** in refluxing 6 M HCl and acetone gives

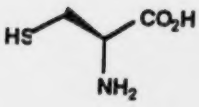
Scheme 11


CO$_2$H
NH$_2$
30
COCl$_2$
O
HN
O
O
32
20
H$_2$N
H
N
CO$_2$CH$_3$
O
CH$_3$
33
Δ
61 %
H
N
O
O
N
H
34
(CH$_3$)$_3$O$^+$
BF$_4^-$
66 %
N
OCH$_3$
CH$_3$O
N
35
BuLi
CH$_2$Br$_2$
49 %
N
OCH$_3$
CH$_3$O
N
Br
36
PhCH$_2$SK
78 %
N
OCH$_3$
CH$_3$O
N
S
Ph
37
Hydrolysis
11 %
PhCH$_2$S
CO$_2$CH$_3$
NH$_2$

31


H
N
OCH$_3$
CH$_3$O
N
S
Ph

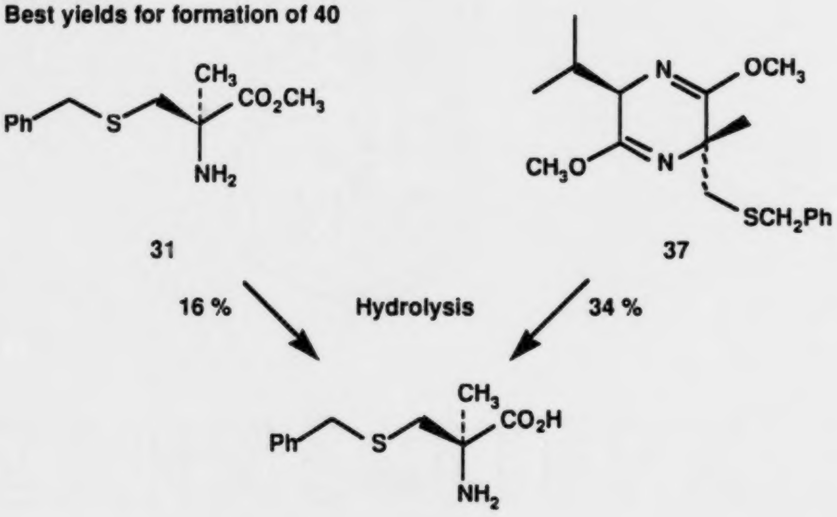
38



39

the desired α-methyl amino acid **40** in 35 % yield (based on recovered starting material) after ion exchange chromatography (Scheme 12). Even after 75 min reaction time, the starting material was only approximately 40 % consumed. An amino acid derivative that is so resistant to hydrolysis may ultimately provide a peptide based drug which can be orally effective. Dilute base hydrolysis of **31** gives the amino acid **40** in only 11 % yield. In contrast, iodotrimethylsilane reacts with **31** to give **40** in 20 % yield.

Scheme 12
Best yields for formation of 40



40
41 Enantiomer

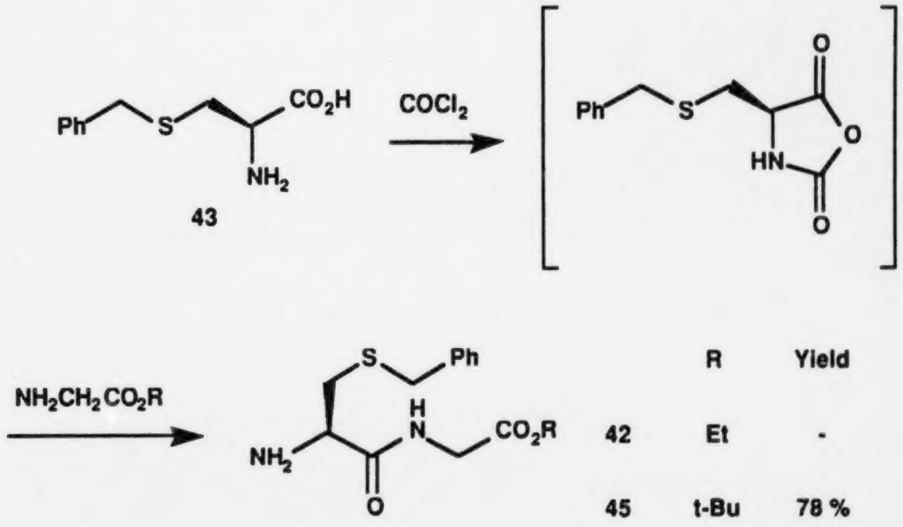
Compound 41 was formed analogously from 16

Since yields for the two stage hydrolysis were low, cleaveage of the bis-lactim ether **37** to the parent amino acids followed by separation of the products was investigated. Compound **37** hydrolyses in 0.25 M HCl over 12 days as described in Schöllkopf's procedure[47] which was modified by using acetonitrile as cosolvent. A solution of 2 M NaOH hydrolyses the unseparated mixture of resulting methyl esters to (*R*)-valine and **40**. Separation of the two amino acids with ion exchange and MPLC reversed phase chromatography gave the desired compound **40** in only 2 % isolated yield. The material is insoluble in the mobile phase creating difficulties during MPLC. The yield can be improved to 34 % by reaction of **37** with refluxing concentrated HCl and separation by ion exchange chromatography. This method gives the highest yield for the preparation of **40** (from **37**: 6 M HCl, overall yield 34 %; dilulte HCl, then NaOH, overall yield 16 %).

With the α-methyl amino acid available, coupling protocols were investigated. In 1953, Rudinger & Sorm prepared cysteinylglycine ethyl ester **42** using *S*-benzylcysteine (**43**) via the *N*-carboxyanhydride (Leuch's anhydride) route.[48] Kaminski and co-workers suggest that the same method gives high yields and pure products for α,α-disubstituted amino acid couplings.[49] In a test coupling procedure, shown in Scheme 13, **43** reacts with phosgene and subsequently glycine *t*-butyl ester (**44**) to give the protected dipeptide **45** in 78 % yield.

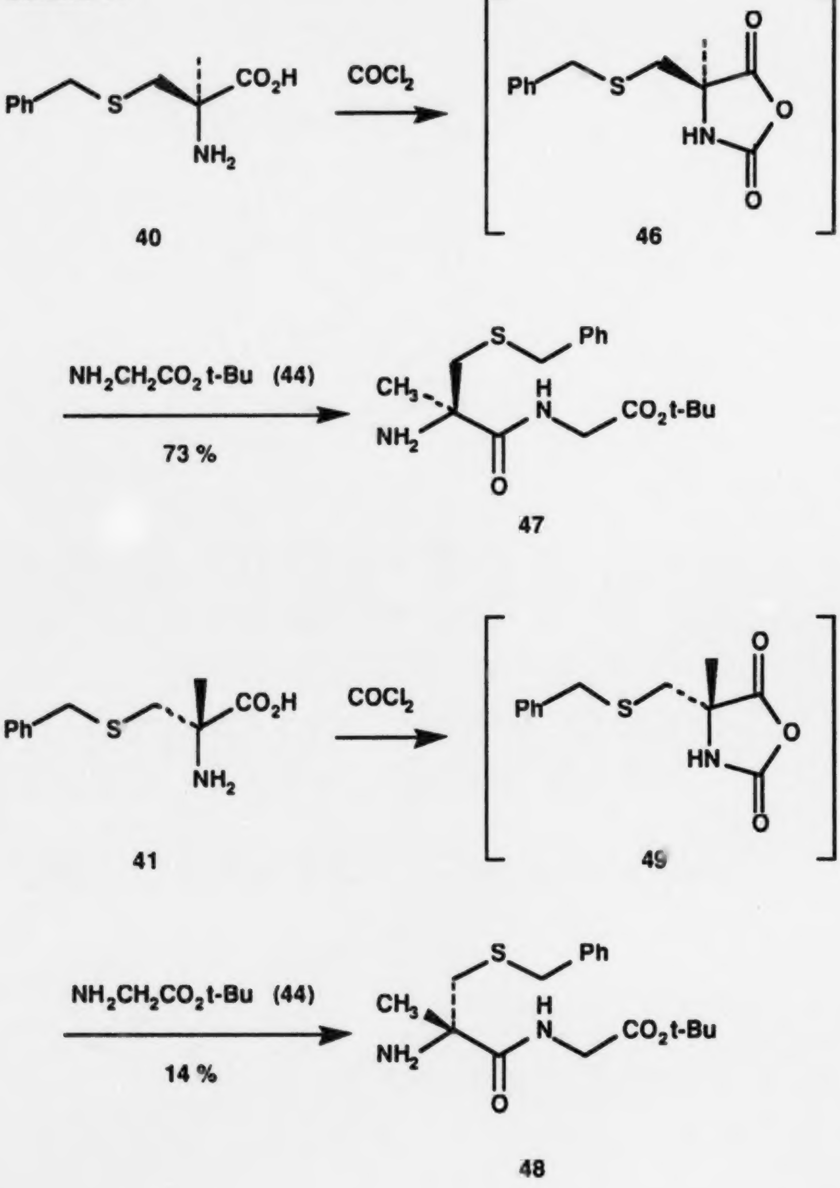
These results encouraged use of the Leuch's anhydride procedure with the α-methyl amino acids. Initial attempts used pure *S*-benzyl-α-methylcysteine (**40**), but only

Scheme 13



limited quantities were available. The crude hydrolyzate of **40** (mass balance 124 % from **31**) condenses with phosgene to give the *N*-carboxyanhydride intermediate **46** (Scheme 14) which then reacts *in situ* with **44** to generate *S*-benzyl-α-methylcysteinylglycine *t*-butyl ester **47** in 73 % yield from **31**. Likewise **41** (prepared from **16** in 34 % yield) gives the

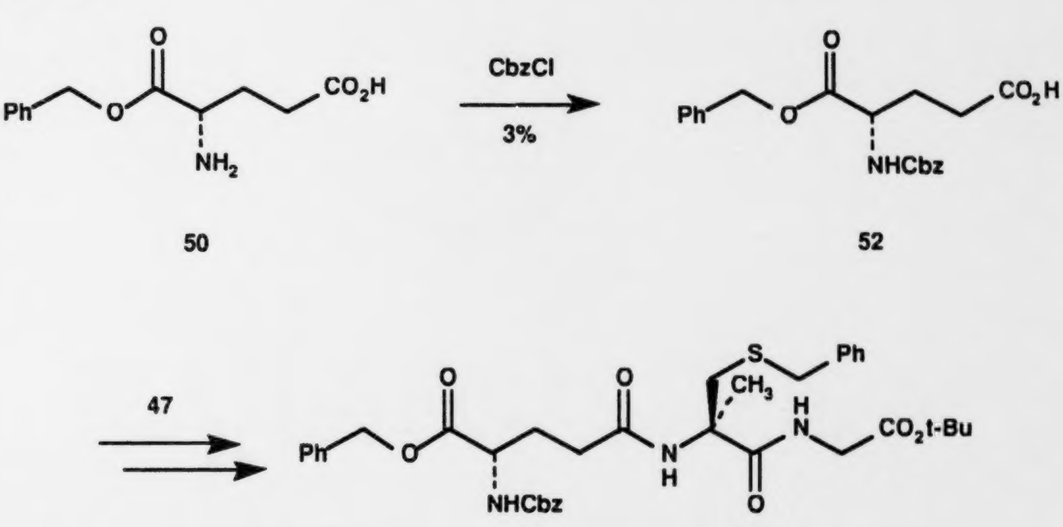
Scheme 14


Ph
S
CO2H
NH2
COCl2
O
HN
40
46
NH2CH2CO2t-Bu (44)
73 %
CH3
NH2
H
N
CO2t-Bu
47
41
49
14 %
48

enantiomeric dipeptide ester **48** via the *N*-carboxyanhydride **49**.

Investigations for transformation of the dipeptides into tripeptides employed two possible routes. The first of these begins with commercially available α-benzyl (*S*)-glutamate (**50**). Amine protection with the carbobenzyloxy group, activation of the γ-carboxyl group, and addition of the dipeptide **47** would form the glutathione analogue **51**. Examination of this method (Scheme 15) shows that the first reaction, benzyloxycarbonyl protection of the amine to produce the protected glutamate **52**, proceeds in only 3 % yield.

Scheme 15



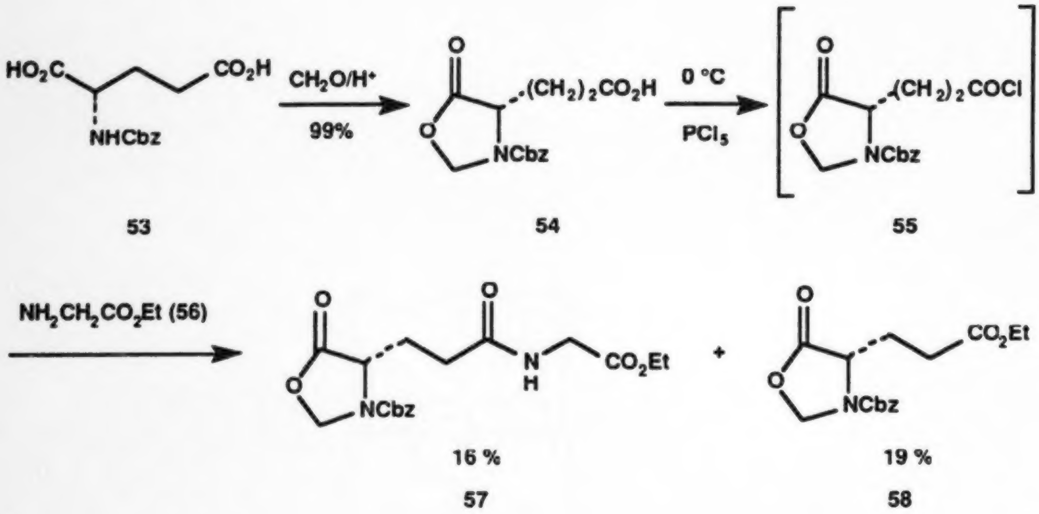
50

52

51

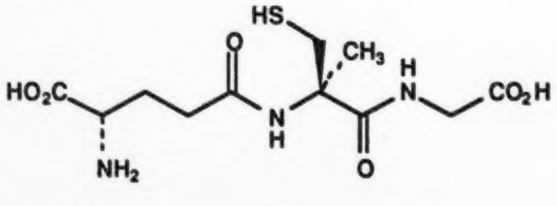
An alternative approach uses *N*-carbobenzyloxy-(*S*)-glutamic acid (**53**) as starting material.[50, 51] Compound **53** reacts with formaldehyde under acidic conditions to give the oxazolidinonepropanoic acid **54** in 99 % yield (Scheme 16). Treatment of **54** with PCl_5 at 0 °C generates the unstable acid chloride **55**. To test its coupling to amino esters, readily available glycine ethyl ester (**56**) was used. Thus, the acid chloride **55** reacts with **56** to give the protected glutamylglycine **57** in 16 % yield. Interestingly, the glutamyl

Scheme 16

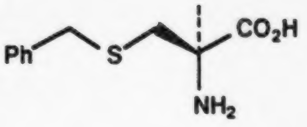


ethyl ester derivative **58** was isolated in 19 % yield, perhaps because of ethanol present as an impurity in the starting glycine ester **56**. However, the total yield of products **57** and **58** is only 35 % thereby implying that the acid chloride **55** may have been formed only in low yield.

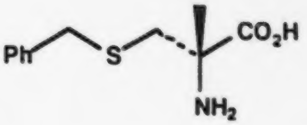
Although these studies produced both enantiomers of the α-methylcysteine **40** and **41** as well as their glycine dipeptides **47** and **48** in protected form, synthesis of glutathione analogue **59** and its isomers was not continued. Because of low yields, the dipeptides **47** and **48** are available in very limited amounts. Due to steric hindrance the



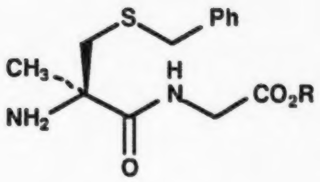
59



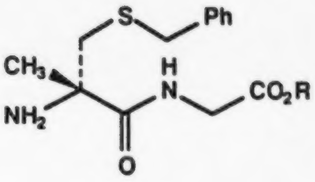
40



41



47



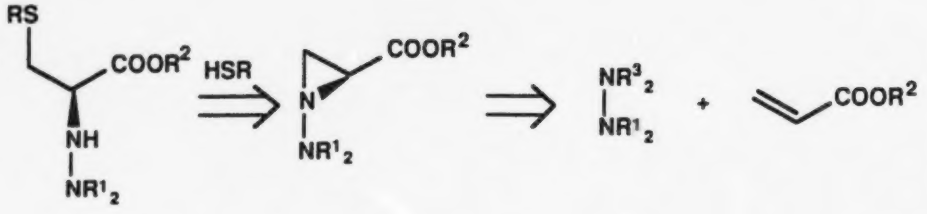
48

yields for coupling procedures will probably also be low. Even after coupling, final deprotection by ester hydrolysis[52] and *S*-benzyl group removal[53] would be required before coupling to LTA$_4$ derivatives. Hence, the four key compounds **40**, **41**, **47** and **48** were reserved for deprotection and biological testing. Future research will focus on the area of introducing these amino acid derivatives into LT skeletons.

3. Hydrazinocysteines

Although there are many preparations for hydrazino acids, only a few produce optically pure compounds and most are incompatible with the sensitive thiol or sulfide group of cysteine derivatives.[54-59] A retrosynthetic analysis for hydrazinocysteine is shown in Scheme 17. The hydrazino acid skeleton could in theory be elaborated from a di-*N*-protected amino aziridine using a nucleophilic sulfur reagent. Such a three membered ring might be formed from an acrylate and an amino-nitrene derived from a hydrazine derivative. This route should allow for modifications to the cysteine skeleton by choice of substitution pattern in the acrylate. Once the desired skeleton is formed, the nitrogen-

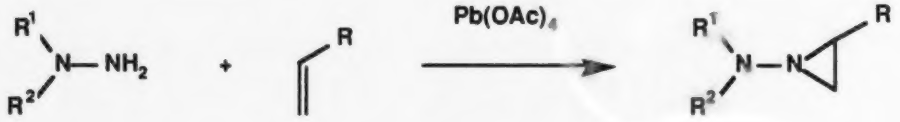
Scheme 17


RS
COOR²
HSR
NH
NR¹₂
N
COOR²
NR¹₂
NR³₂
NR¹₂
+
COOR²

nitrogen bond can be cleaved by standard methods,[60] thereby allowing access to a variety of optically pure sulfur-containing amino acids.

In 1970, Rees and co-workers published the oxidative cycloaddition of *N*-aminophthalimide to alkenes to give *N*-protected aziridines (Scheme 18).[61] This work was followed by many studies of the reaction and its mechanism.[62-67] The type of nitrogen containing species may vary greatly provided that R^1 and R^2 are either non-enolizable carbonyl groups or aromatic rings.

Scheme 18


R¹
N— NH₂
R²
+
R
Pb(OAc)₄
R¹
N—N
R²
R

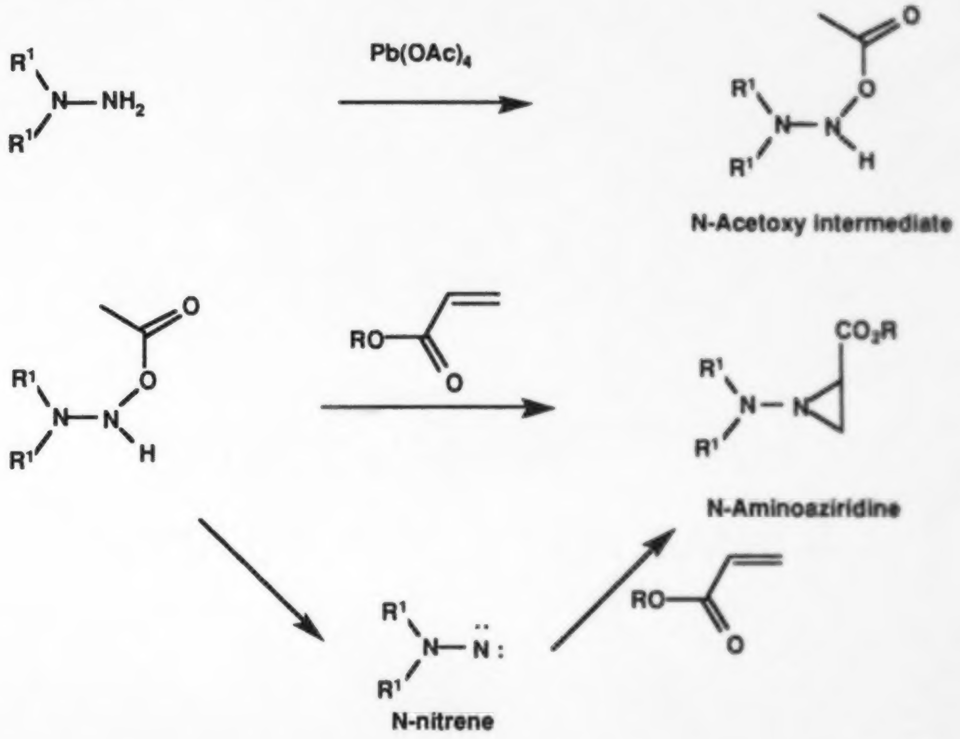
R = Ester, Alkene, Vinyl

R¹= Carbonyl, Aromatic

Atkinson and Kelly proposed a mechanism for the oxidation of *N*-amino derivatives and subsequent reaction with alkenes shown in Scheme 19.[68] The *N*-acetoxy intermediate can react with alkenes to give *N*-aminoaziridines directly, or may form a nitrene which adds to the double bond.

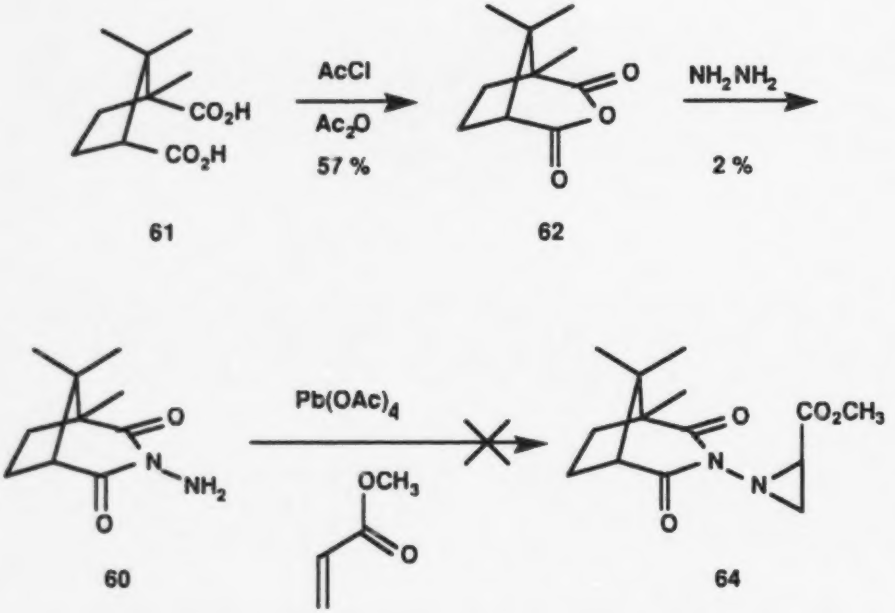
One chiral version of this reaction has been reported.[69] An asymmetric addition of this type could occur with a chiral nitrogen-containing "aziridinating" reagent and an achiral alkene, a chiral alkene and an achiral aziridinating reagent, or with both partners being chiral.

Scheme 19


R1
N—NH2
R1
Pb(OAc)4
R1
N—N
R1
O
O
H
N-Acetoxy intermediate
RO
O
CO2R
N-Aminoaziridine
N—N:
N-nitrene

To investigate the first possibility, the enantiomerically pure *N*-aminocamphorimide (**60**) was prepared as an aziridinating reagent (Scheme 20).[70] Camphoric acid (**61**) reacts with acetyl chloride in acetic anhydride to give camphoric anhydride (**62**) in 57 % yield. Treatment with hydrazine in refluxing 95 % ethanol generates **60** in 2 % yield. Lead tetraacetate oxidation of **60** in the presence of methyl acrylate **63** produces a mixture of products that is unstable to chromatography, and does not appear to contain **64** based on ^1H NMR spectra.

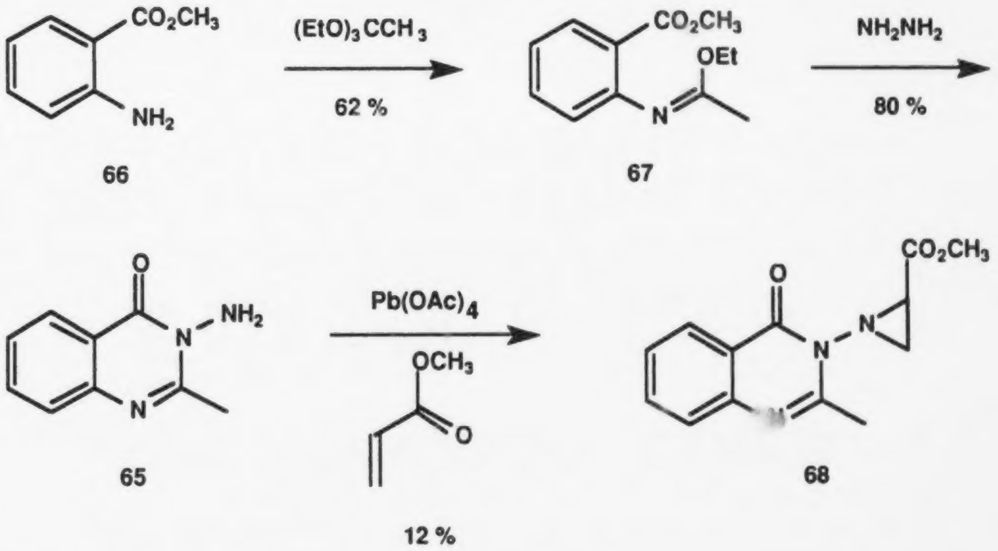
Scheme 20



Since the protected nitrogen must bear non-enolizable carbonyl or aryl groups and is some distance away from the reacting nitrogen, design of an asymmetric aziridinating agent appeared problematic. Hence, the condensation of readily available achiral aziridinating reagents with optically pure acrylates was investigated. Initial studies employed a completely achiral system to examine the feasibility of this approach to α-hydrazino acids.

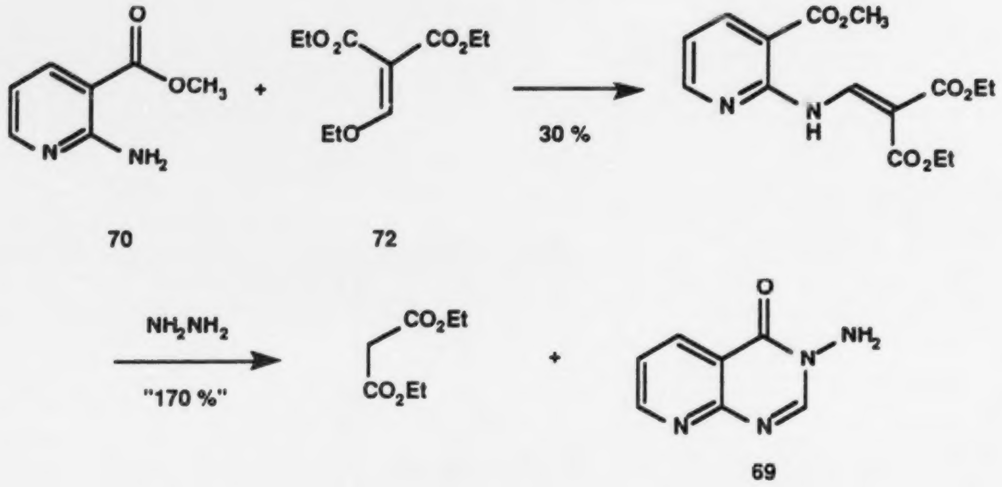
The quinazolone **65** was prepared according to the literature procedure (Scheme 21).[71] Thus, methyl anthranilate (**66**) reacts with triethyl orthoacetate to give the acetimidate **67** in 62 % yield. Reaction with hydrazine gives 3-amino-2-methylquinazolin-4(3H)-one (**65**) in 80 % yield. Treatment of this compound with lead tetraacetate in the presence of methyl acrylate (**63**) affords methyl *N*-(2'-methylquinazolin-4'(3'H)onyl)aziridine-1-carboxylate (**68**) in 12 % yield. This aziridine provides a substrate for investigation of reactions with sulfur containing nucleophiles. However, it is unclear if the quinazolone ring can ever be fully cleaved to give the desired hydrazino group. One hydrolysis attempt with HCl (0.5 M) and **65** yielded, after several weeks, a complex mixture of products more polar than anthranilic acid.

Scheme 21



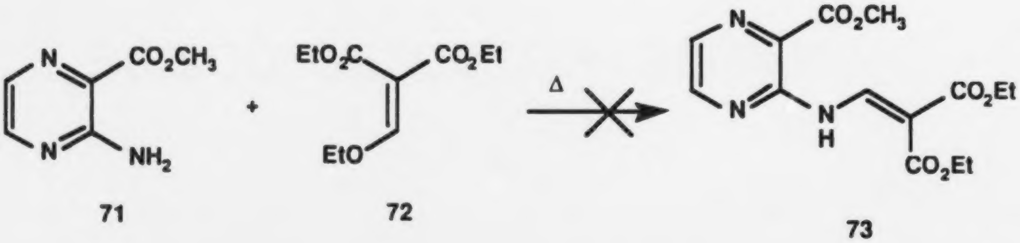
A literature report describes the preparation of 3-aminopyridopyrimidin-4(3H)one **69** (Scheme 22).[72] This compound could be an effective aziridinating reagent, whose ring system may be susceptible to hydrolysis. However, the required starting material, methyl 2-aminopyridine-3-carboxylate (**70**), is not readily available.

Scheme 22


O
OCH$_3$
NH$_2$
N
EtO$_2$C
CO$_2$Et
EtO
30 %
CO$_2$CH$_3$
N
H
CO$_2$Et
CO$_2$Et
70
72
NH$_2$NH$_2$
"170 %"
CO$_2$Et
CO$_2$Et
O
NH$_2$
N
N
N
69

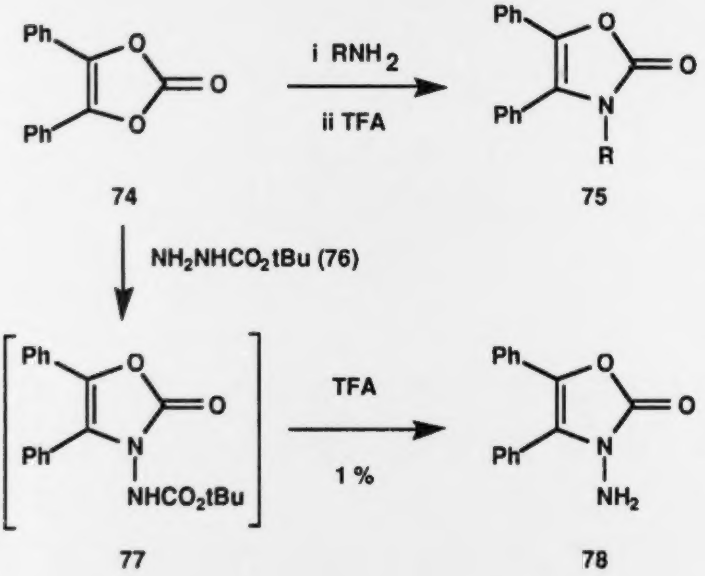
A related compound, methyl 2-amino-3-pyrazinecarboxylate (**71**) could potentially form an analogous ring system (Scheme 23). However, **71** does not react with **72**, and none of the expected **73** was isolated. This result suggests the amino group of **71** is not as nucleophilic as the amine of **70**, possibly due to the inductive withdrawing effect of the extra ring nitrogen.

Scheme 23


N
CO$_2$CH$_3$
N
NH$_2$
71
EtO$_2$C
CO$_2$Et
EtO
72
Δ
N
CO$_2$CH$_3$
N
N
H
CO$_2$Et
CO$_2$Et
73

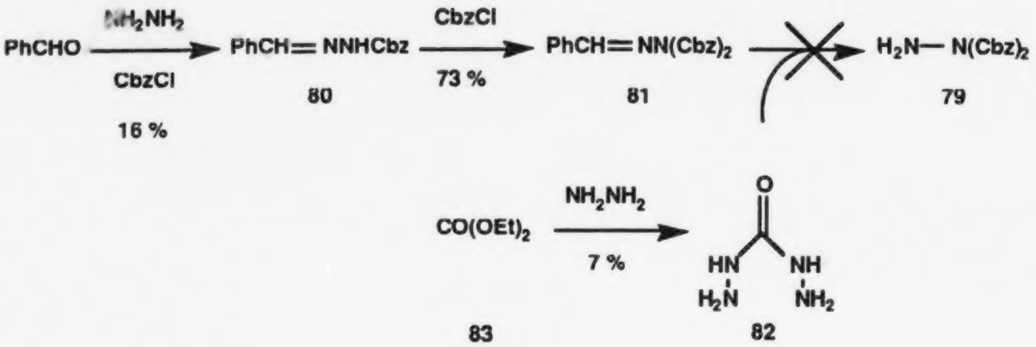
Attention next focussed on a literature procedure in which amine nucleophiles react with 4,5-diphenyldioxol-2-one (**74**) to form oxazolones **75** (Scheme 24).[73] *t*-Butyl carbazate (**76**) reacts with **74** to generate **77** which is immediately deprotected with trifluoroacetic acid (TFA) to give an unstable product **78** in 1 % yield. Although **78** has potential as an aziridinating reagent, it is sensitive to light in addition to being formed in very low yield. These factors make it unsuitable as a starting material.

Scheme 24



Milcent and co-workers reported the reaction of 1,1-dibenzyloxycarbonylhydrazine (**79**) with alkene solvents[74] under conditions derived from those developed by Rees and co-workers (Scheme 25).[61] The aziridinating reagent **79** was prepared in three steps from benzaldehyde. The aldehyde reacts with hydrazine and benzyl chloroformate to give **80** in 16 % yield. Hydrazone **80** condenses with benzyl chloroformate again to give **81** in 73 % yield. Finally, deprotection employs carbohydrazide (**82**), which is prepared from diethyl carbonate (**83**) and hydrazine in 7 % yield.[75] Unfortunately, the carbohydrazide (**82**)

Scheme 25

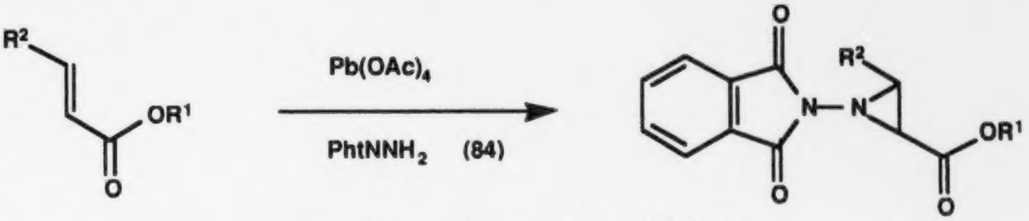


proved to be contaminated with unknown impurities, which were difficult to remove and interfered with the deprotection of **81**. Since further attempts to purify the hydrazide proved unsuccessful and the literature report required a large excess of alkene to trap the aziridinating species,[74] this route would require a large excess of chiral acrylate and appeared unfeasible.

The remaining aziridinating reagent which was investigated was the commercially available *N*-aminophthalimide (**84**). This compound is only slightly soluble in dichloromethane and provides a low concentration of reactive intermediate under oxidative conditions, thereby decreasing the chance of undesirable side reactions.[76] The oxidation of **84** with lead tetraacetate occurs rapidly, the process is well understood already, and the reaction occurs with many alkenes including acrylates. Furthermore, the removal of the phthalimido group proceeds readily.[36]

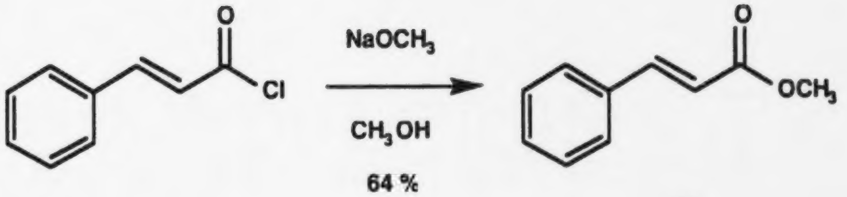
The results of our initial test aziridination reactions with (**84**) are summarized in Table 1. (E)-Methyl cinnamate (**85**), prepared from cinnamoyl chloride in 64 % yield (Scheme 26), reacts with **84** and lead tetraacetate to give methyl 3-phenyl-*N*-phthalimidoaziridine-2-carboxylate (**86**) in 48 % yield. Ethyl acrylate (**87**) and methyl acrylate (**63**) form the corresponding ethyl or methyl aziridine-2-carboxylates (**88**) and (**89**), respectively.

Table 1


R2
OR1
O
Pb(OAc)4
PhtNNH2 (84)
O
R2
N
N
OR1
O
O

Starting material	Product	R1	R2	Yield %
85	86	CH_3	Ph	48
87	88	Et	H	34
63	89	CH_3	H	51

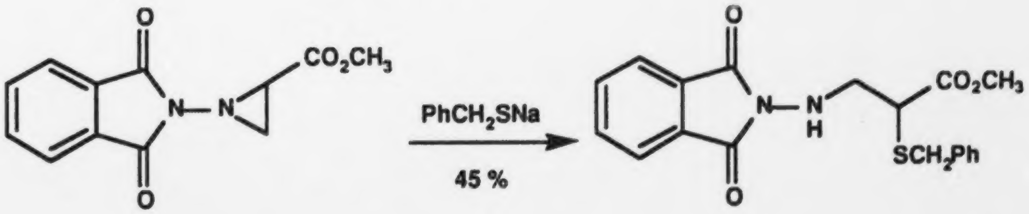
Scheme 26


O
Cl
NaOCH3
CH3OH
64 %
O
OCH3

85

To determine whether the protected *N*-aminoaziridines would provide a feasible route to hydrazinocysteines, aziridine **89** was treated with sodium benzylthiolate.

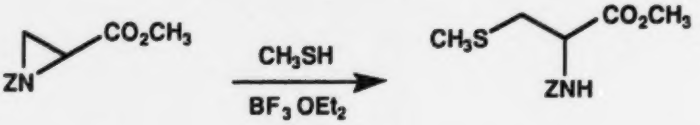
Scheme 27


O
N
N
CO2CH3
O
PhCH2SNa
45 %
O
N
N
H
CO2CH3
SCH2Ph
O

89

90

Reaction occurs at the α-carbon to give *S*-benzyl-*N*-phthalimidoisocysteine methyl ester (**90**) in 45 % yield (Scheme 27). No attack at the less hindered β-carbon could be detected. Several reports suggest that Lewis acids favour nucleophilic attack at the β-carbon of *N*-aryl aziridines to produce β-substituted amino acids.[77-80] In 1977, Bernstein and Ben-Ishai reported that methyl (*RS*)-*N*-benzyloxycarbonylaziridine-2-carboxylate (**91**) opens to give methyl (*RS*)-*N*-benzyloxycarbonyl-*S*-methylcysteinate (**92**) in 80 % yield.[81] The *N*-aminoaziridine **88** reacts analogously with methane thiol and boron trifluoride etherate to generate a mixture of regioisomers: the protected hydrazino-isocysteine **93** and the protected hydrazino-cysteine **94** in 9 % and 5 % yield, respectively (Scheme 28). These two compounds are surprisingly difficult to separate, but repeated (3 X) MPLC gives pure samples.

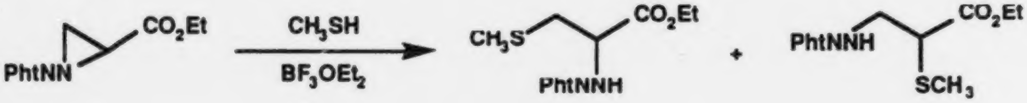


91

92

Although analogous reactions of the corresponding methyl ester **89** proved problematic, the aziridine **86** derived from methyl cinnamate (**85**) reacts with *p*-meth-

Scheme 28

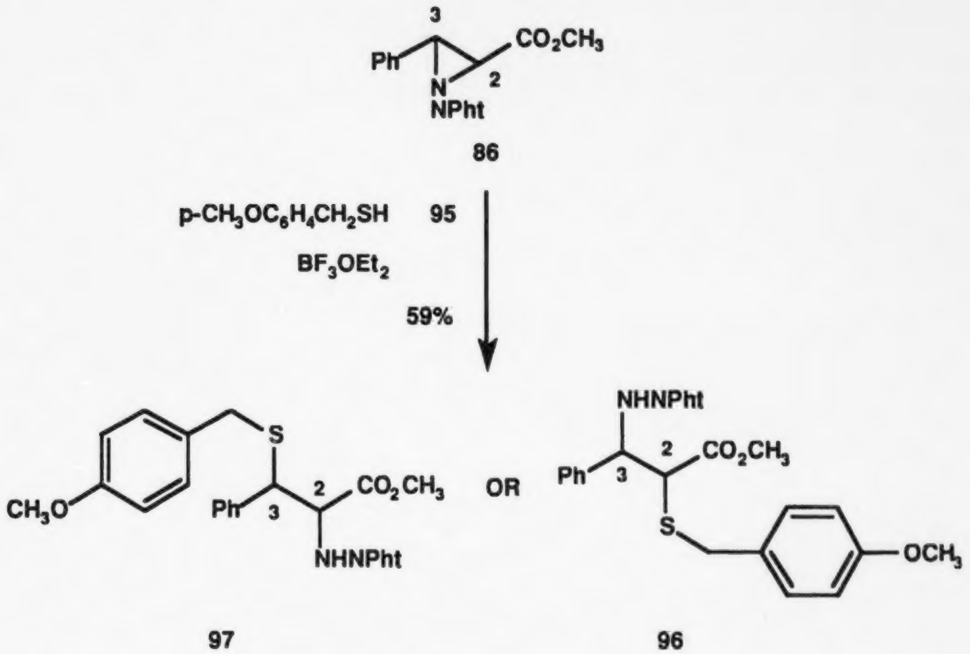


88

94
5 %

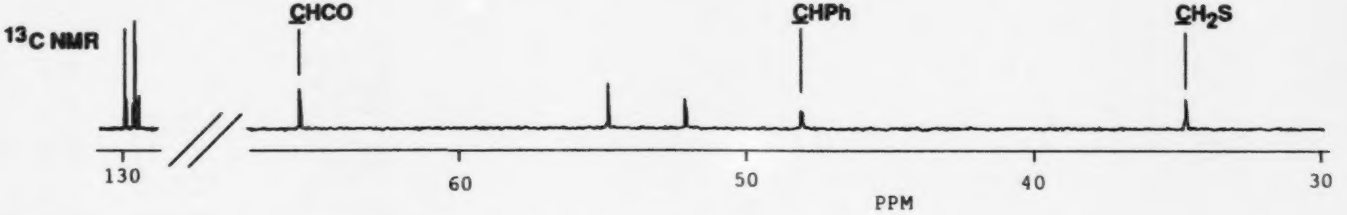
93
9 %

Scheme 29

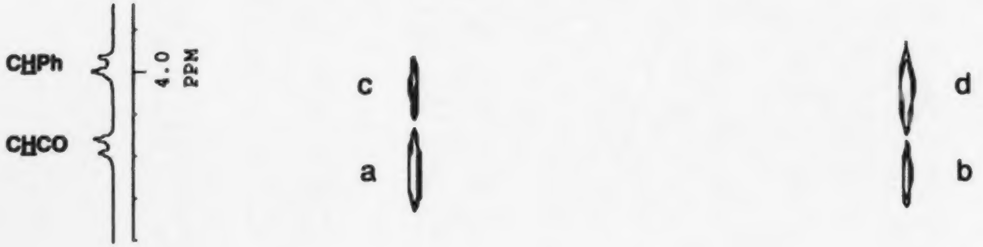


oxybenzylthiol (**95**) and boron trifluoride etherate to give a single regioisomer in 59 % yield (Scheme 29). To determine whether regioisomer **96** or **97** was produced, detailed ^{1}H-^{13}C heteronuclear correlation (hetcor) NMR studies were done (Figure 2). The upper two dimensional spectrum is a section of the normal hetcor which shows cross peaks for short range (a,d) and long range (b,c) couplings. The lower BIRDTRAP spectrum is a long range hetcor experiment in which the directly bonded C-H correlations are suppressed. Most important are the key cross peaks e and f. Cross peak e results from a phenyl carbon coupling with the β-H. Cross peak f results from long range coupling between the *p*-methoxyphenylmethyl carbon and the same β-H. This suggests that the sulfur nucleophile has attacked at the β position which bears the phenyl ring. Thus, the BIRDTRAP experiment suggests that the hydrazino cysteine derivative **97** was formed in the reaction of **86** with **90** in the presence of boron trifluoride etherate.

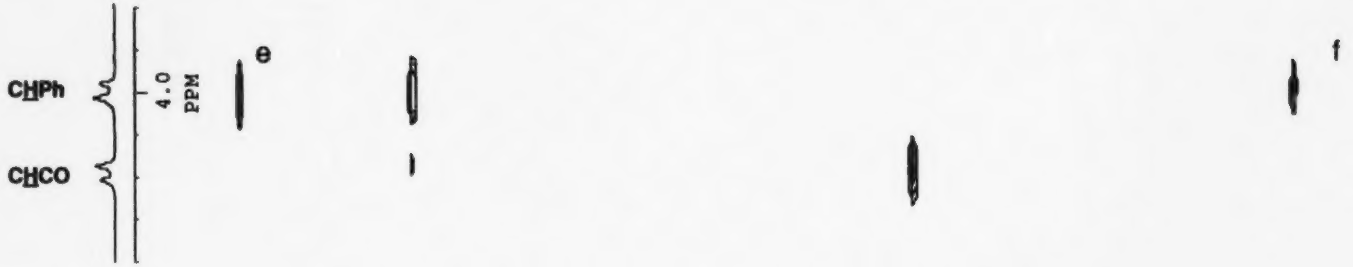
Figure 2. Heteronuclear correlation spectra for compound 97



^{1}H - ^{13}C Heteronuclear correlation spectrum

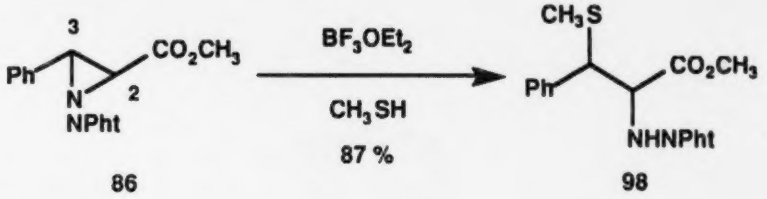


^{1}H - ^{13}C Long range heteronuclear correlation BIRDTRAP



Compound **86** reacts analogously with methanethiol and boron trifluoride etherate to give derivative **98** in 87 % yield (Scheme 30). Thus, the reaction of *N*-aminoaziridines with thiols appeared to be a promising method for the preparation of hydrazinocysteines, especially because procedures for removal of *S*-benzyl and *N*-phthalimido groups are available.[36]

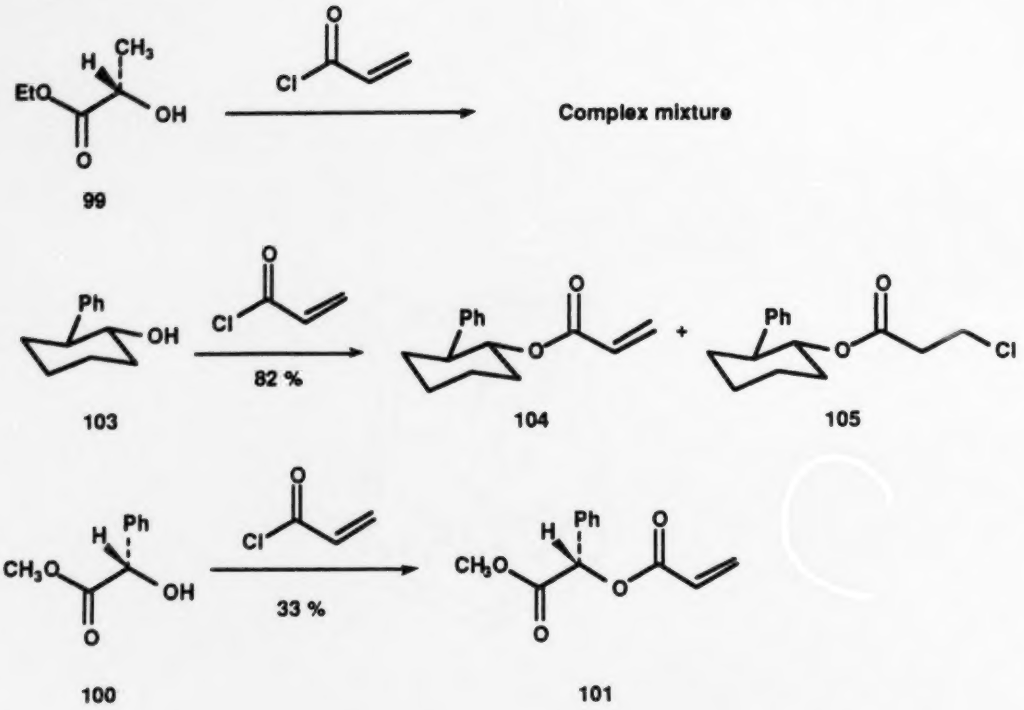
Scheme 30



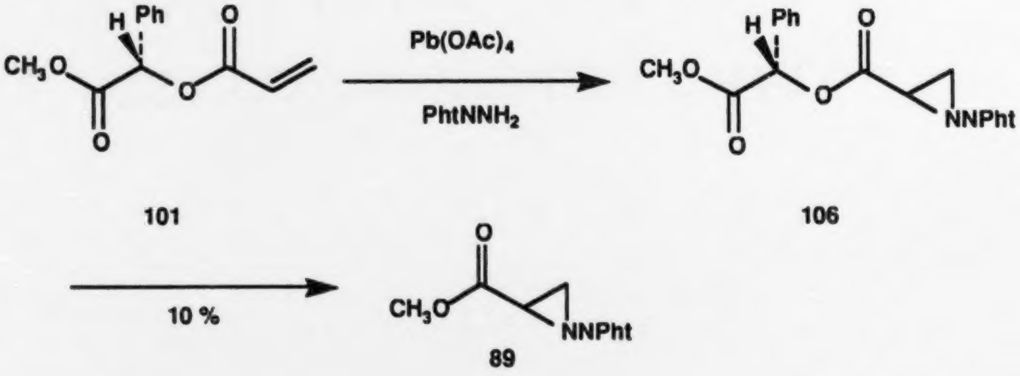
The next objective was to identify a chiral auxiliary which could be attached to the acrylate moiety to afford high stereoselectivity in the aziridination reaction. Initial studies centred on acrylate esters of chiral alcohols (Scheme 31). Although reaction of acryloyl chloride with ethyl lactate (**99**) produces a complex mixture, methyl (*S*)-mandelate (**100**) gives the corresponding ester **101** in 33 % yield under similar conditions. The (1*R*,2*S*)-phenylcyclohexanol **103** (prepared by Dr. Patricia Lane-Bell according to literature procedures[82]) reacts similarly to afford a mixture (82 % yield) of acrylate **104** and the corresponding 3-chloropropanoate **105**.

Lead tetraacetate oxidation of *N*-aminophthalimide (**84**) in the presence of **101** gave the expected aziridine **106**, which proved difficult to purify (Scheme 32). During the recrystallization of this material from $CH_3OH/CHCl_3$, colourless crystals of the corresponding methyl ester **89** precipitated. This material has a small optical rotation (+4°) which suggests that some diastereoselection occurs during the reaction. However, ^1H NMR studies using europium (III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato

Scheme 31

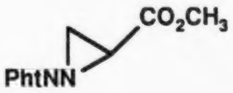

99
Complex mixture
82 %
103
104
105
33 %
100
101

Scheme 32


Pb(OAc)₄
PhtNNH₂
101
106
10 %
89

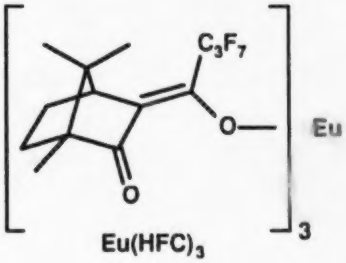
(Eu(HFC)3) showed **89** to be nearly racemic. Figure 3 shows part of the ^{1}H NMR spectrum in which the methyl protons of both conformations of **89** are resolved for both enantiomers. The poorly resolved signals *a* and *b* result from the chiral shift reagent (CSR) complexed with both enantiomers of the major conformation. Signals *c* and *d* are due to the CSR complexed to both enantiomers in the minor conformation. It is possible that the reaction occurs with high selectivity but the enantiomeric purity may be lost during recrystallization and transesterification. Further attempts to purify **106** were unsuccessful.

Figure 3



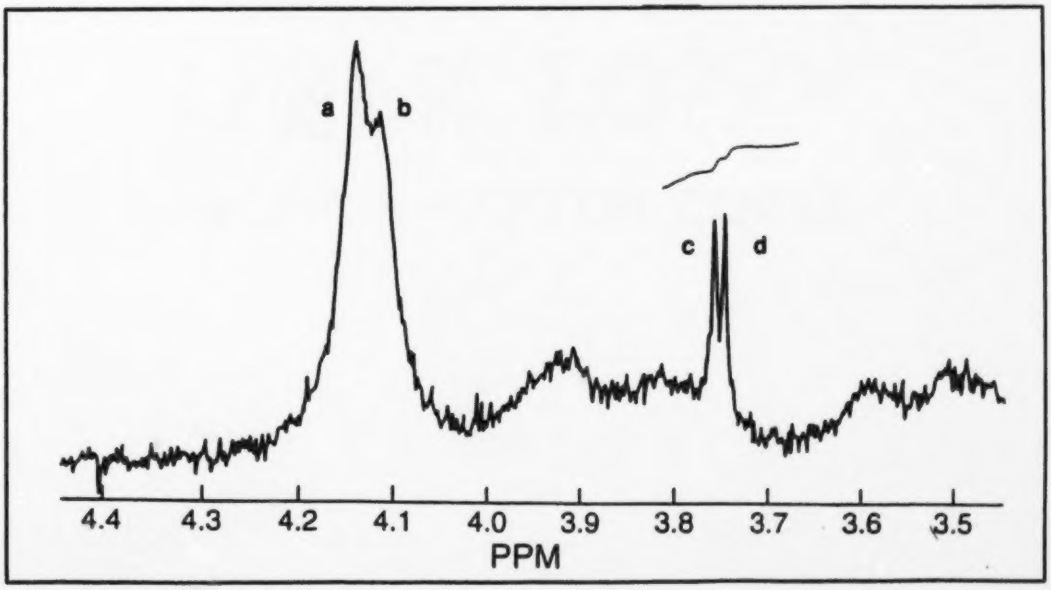
89 from 106

Small optical rotation



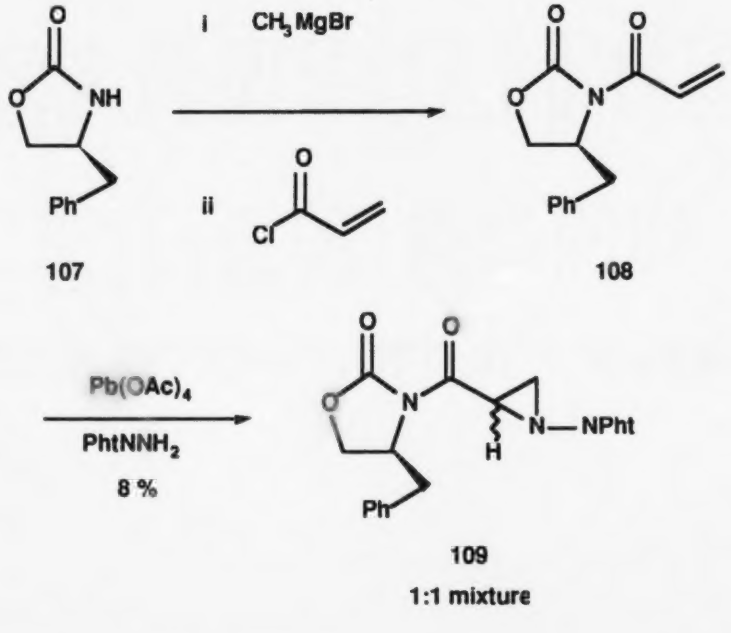
Eu(HFC)$_3$

Partial ^{1}H NMR of 89 and Eu(HFC)$_3$



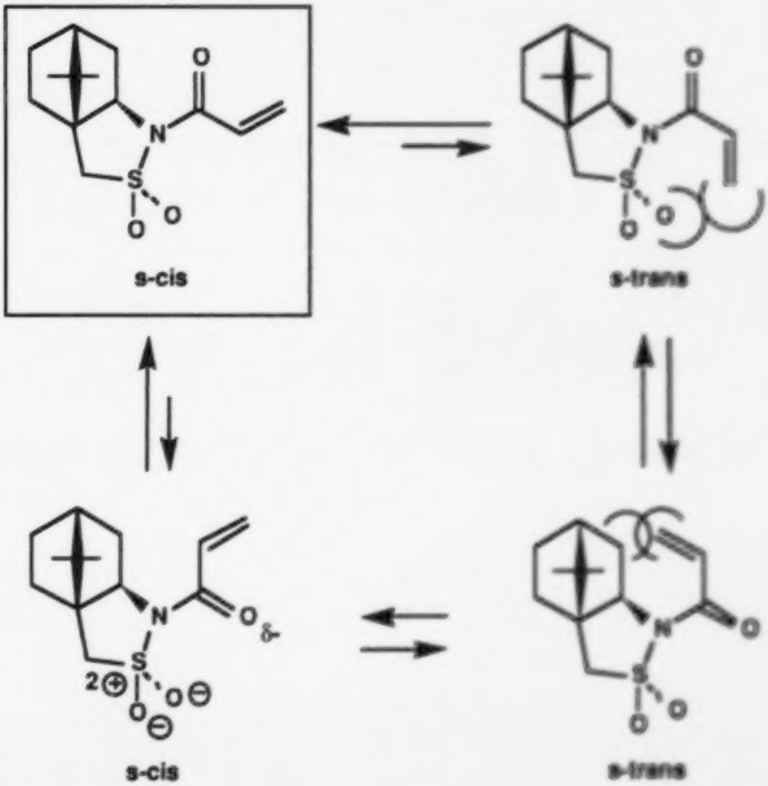
Since amides are conformationally more restricted than esters, they are frequently more successful as chiral auxiliaries. Evans has demonstrated the effectiveness of the commercially available oxazolidinone **107** derived from phenylalanine (**12**) as a chiral auxiliary for stereospecific Lewis acid controlled Diels-Alder reactions.[83] Oxazolidone **107** reacts with acryloyl chloride to give the known propenamide **108** in 67 % yield (Scheme 33). Reaction of *N*-aminophthalimide (**84**) and lead tetraacetate in the presence of Me_2AlCl as Lewis acid gave none of the desired product. Presumably the amine attacks the Lewis acid, thereby interfering with oxidation by lead tetraacetate. However, **108** reacts with **84** in the presence of lead tetraacetate and in the absence of a Lewis acid to give the expected aziridine **109** in 8 % yield. HPLC analysis of the reaction products indicates that a 50:50 mixture of diastereomers is formed.

Scheme 33



The next amide chiral auxiliary tested was the propenamide **110** derived from camphorsultam. Oppolzer has successfully used this compound in Lewis acid catalyzed Diels-Alder additions.[84] Other investigators have since used **110** in 3 + 2 dipolar addition reactions and cyclopropanations, and shown that a Lewis acid is not absolutely necessary for high stereoselectivity.[85-87] As seen in Scheme 34, there are at least four possible conformations which the propenoyl group may adopt. For steric reasons the s-trans conformations are likely to be destabilized. Repulsion of like charges on the dipoles should also destabilize the conformations in which the C=O and S-O bonds are aligned. This analysis suggests that the most favoured conformation may be the s-cis arrangement

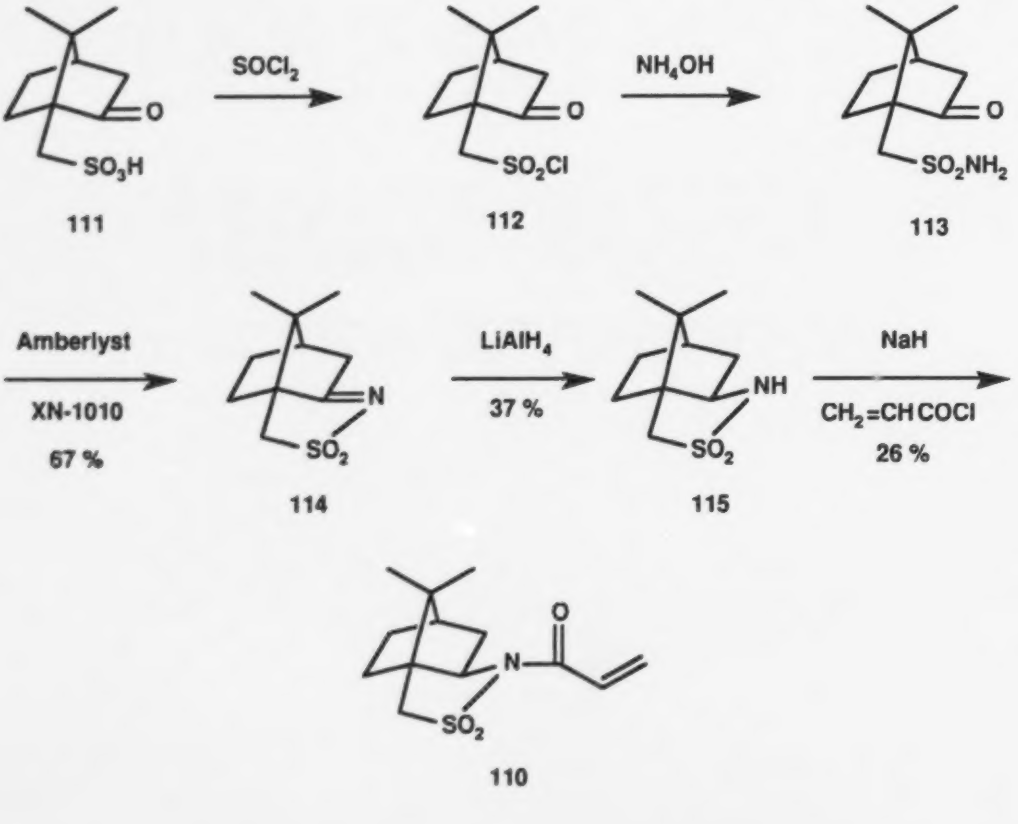
Scheme 34
Four Conformations of 110



displayed in the upper left corner of Scheme 34. Aziridines have been reported to form more readily if the s-cis conformation of alkenes is favoured. For nitrile oxide addition to **110**, the stereochemistry of attack can be rationalized as proceeding on the s-cis conformation from the "gem dimethyl face" of the chiral auxiliary (from above as seen in this perspective).[85]

The camphorsultam is commercially available in both enantiomerically pure forms. However, since multigram quantities for these studies were required, the D isomer was synthesized according to literature procedures.[88, 89] Thus, D-camphorsulfonic acid (**111**) reacts with thionyl chloride to form the intermediate camphorsulfonyl chloride (**112**) which is immediately added to ammonium hydroxide to afford the camphorsulfonamide (**113**) (Scheme 35). Amberlyst ion exchange resin gives the camphorsulfonimine (**114**) in 67 %

Scheme 35


O
SO3H
111
SOCl2
O
SO2Cl
112
NH4OH
O
SO2NH2
113
Amberlyst
XN-1010
67 %
N
SO2
114
LiAlH4
37 %
NH
SO2
115
NaH
CH2=CHCOCl
26 %
O
N
SO2
110

yield for the three steps. Compound **114** reacts with lithium aluminum hydride to produce camphorsultam (**115**) in 37 % yield. The corresponding anion, formed with sodium hydride, condenses with acryloyl chloride to give **110** in 26 % yield.

The propenamide **110** reacts with **84** and lead tetraacetate to give **116** and **117** in 94 % combined yield as an 8:1 mixture of diastereomers (Scheme 36). The major

Scheme 36

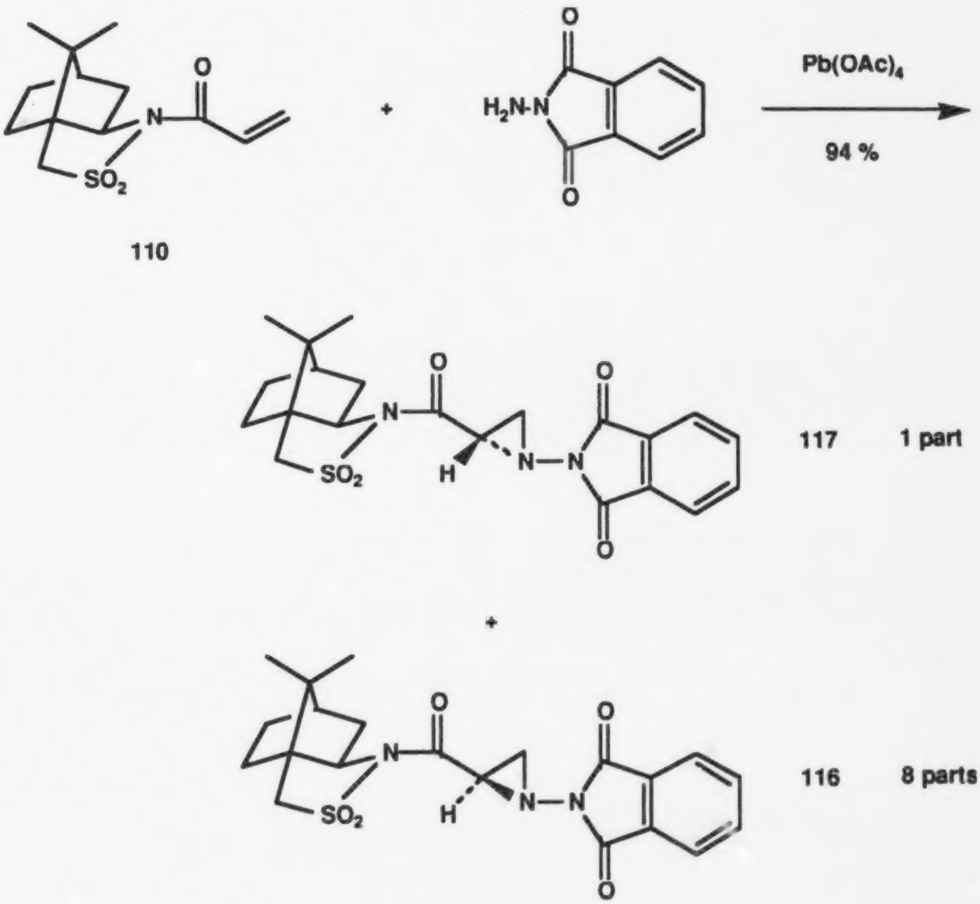
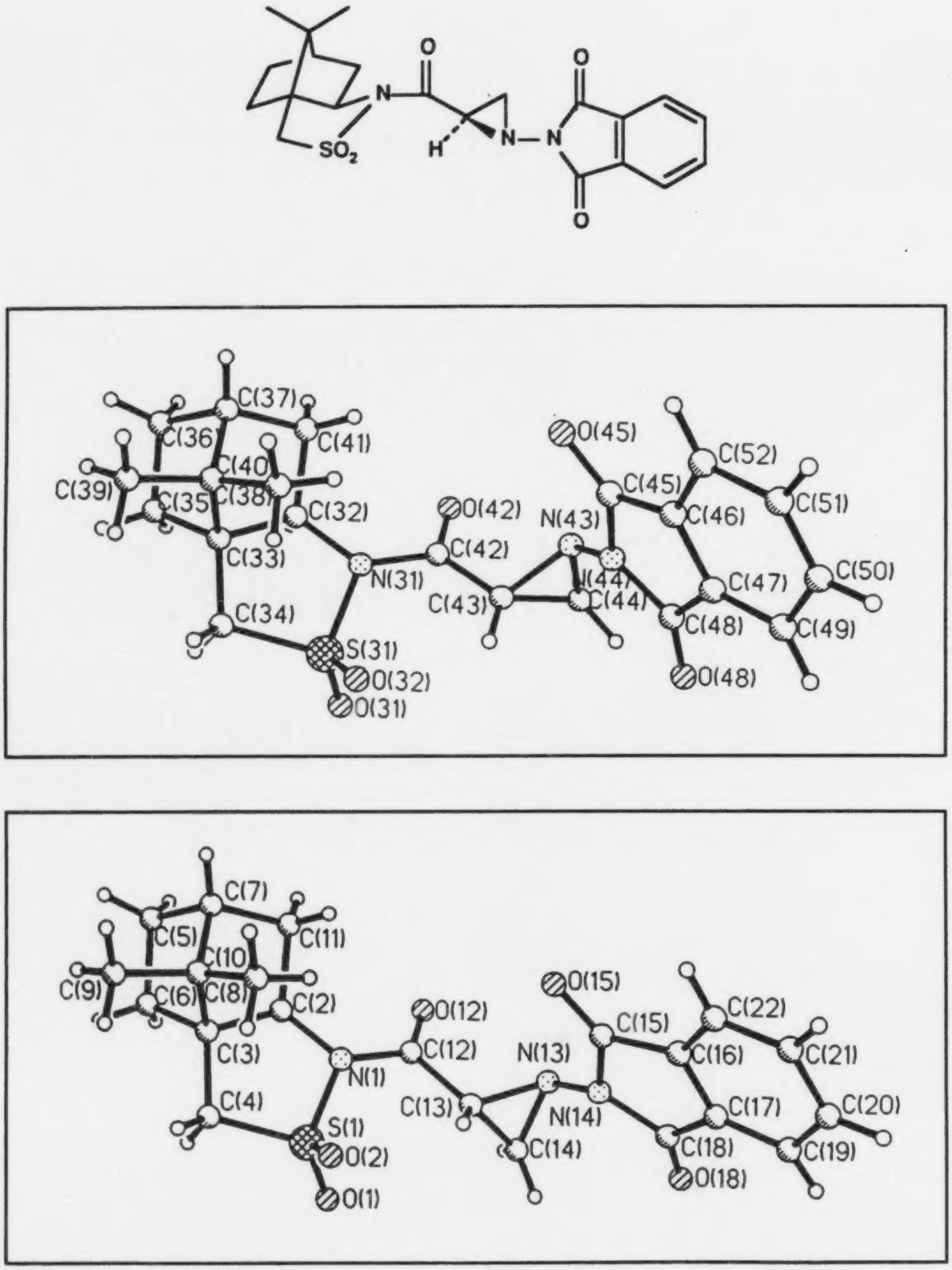

O
N
SO2
+
H2N-N
O
O
Pb(OAc)4
94 %
110
O
N
SO2
H
N—N
O
O
117
1 part
+
O
N
SO2
H
N—N
O
O
116
8 parts

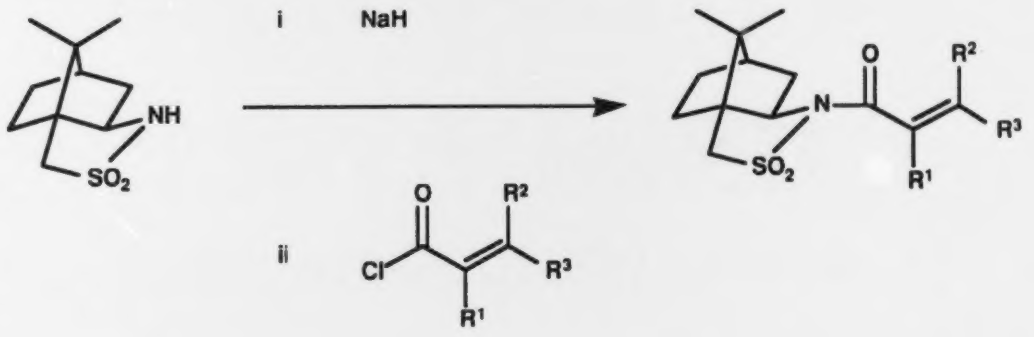
Figure 4
X-ray crystal structures of 116


O
N
SO₂
H
N
N
O
O
C(37)
C(36)
C(41)
C(40)
C(39)
C(38)
C(35)
C(32)
O(42)
C(33)
N(31)
C(42)
N(43)
N(44)
C(43)
C(44)
C(34)
S(31)
O(32)
O(31)
O(45)
C(45)
C(52)
C(46)
C(51)
C(47)
C(50)
C(48)
C(49)
O(48)
C(7)
C(5)
C(11)
C(10)
C(9)
C(6)
C(8)
C(2)
O(12)
C(3)
N(1)
C(12)
N(13)
C(13)
N(14)
C(14)
C(4)
S(1)
O(2)
O(1)
O(15)
C(15)
C(22)
C(16)
C(21)
C(17)
C(20)
C(18)
C(19)
O(18)

isomer **116** crystallizes from toluene and hexanes to give colourless crystals suitable for X-ray analysis (Figure 4). According to the analysis above, the predominant isomer is expected to be formed from phthalimido attack from the "gem dimethyl face" of the sultam (Scheme 34). The X-ray structure of the two conformers present in crystals of **116** (Figure 4) is consistent with this rationale.

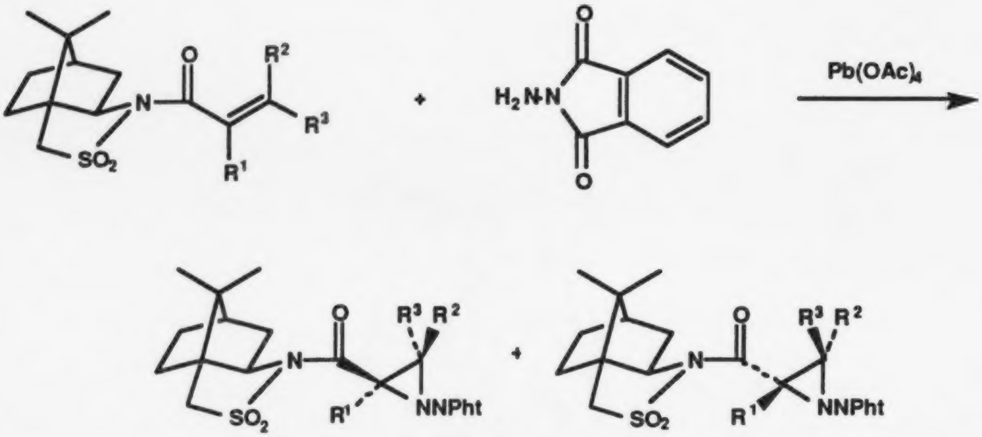
This result encouraged investigation of the potential formation of other hydrazino acid derivatives using various substituted propenamides. (E)-Crotonyl chloride (**118**), (E)-cinnamoyl chloride, 3,3-dimethylacryloyl chloride (**119**) (prepared from the acid **120**) and methacryloyl chloride (**121**) each react with the sodium salt of camphorsultam **115** to give the propenamides in variable yields (Scheme 37). The results of aziridinations with these products are shown in Scheme 38. β-Dimethyl substitution of the acrylamide sultam **124**, lowers the yield of aziridine (67 % vs 94 % yield for the parent **116**), but greatly

Scheme 37



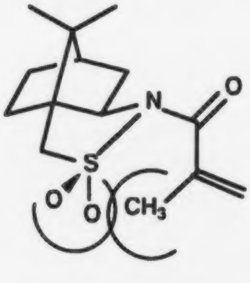
Acid chloride	Propenamide	R^1	R^2	R^3	Yield
Acryloyl	110	H	H	H	26 %
118	122	H	H	CH_3	57 %
Cinnamoyl	123	H	H	Ph	94 %
119	124	H	CH_3	CH_3	10 %
121	125	CH_3	H	H	94 %

Scheme 38


Pb(OAc)$_4$
H$_2$N-N
SO$_2$
R^1
R^2
R^3
NNPht

A B

Propenamide	Aziridine A B	R¹	R²	R³	Yield	Diastereomeric excess of A isomer
110	116 117	H	H	H	94 %	78 %
122	126 127	H	H	CH_3	61 %	33 %
123	128 129	H	H	Ph	90 %	80 %
124	130	H	CH_3	CH_3	67 %	>95 %
125	131 132	CH_3	H	H	12 %	70 %

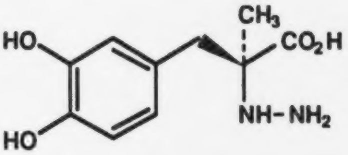


125

Disfavoured

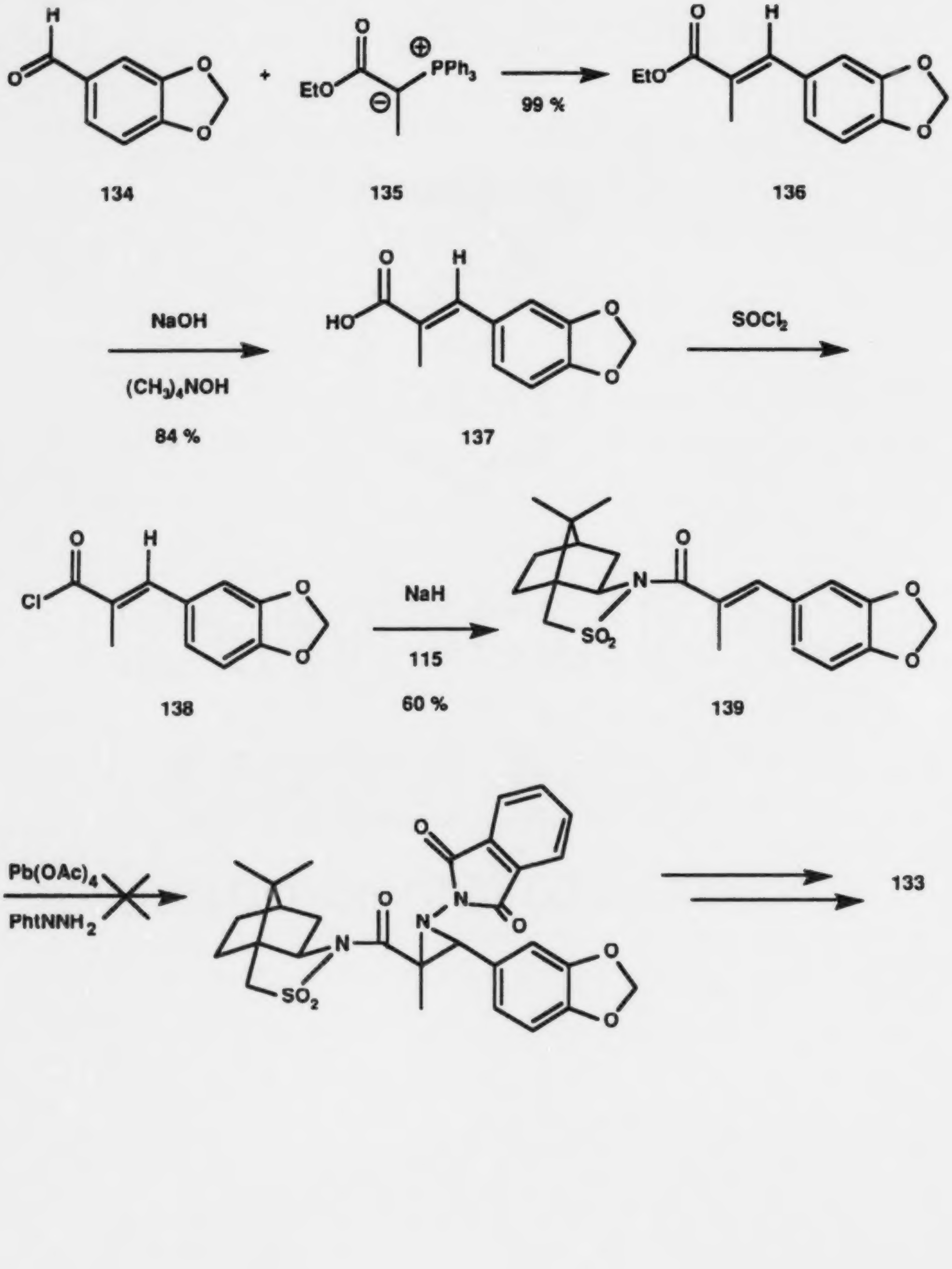
improves the diastereoselectivity of the reaction (only one isomer **130** observed in the ^1H NMR). There is drastic reduction in yield when the α-hydrogen is substituted by a methyl group. A six-fold excess of the methacrylamide sultam **125** reacts with **84** in the presence of lead tetraacetate to form the aziridines **132** and **131** as a 5.7:1 mixture of diastereomers in 12 % overall yield. It is likely that steric repulsion between the oxygen atoms of the sulfonamide and the α-methyl group force the α,β-unsaturated carbonyl moiety out of the s-cis conformation.[90]

The aziridination reaction could provide a route to the neuroactive drug carbidopa (**133**). Carbidopa is used in the treatment of Parkinson's disease,[91] and a new stereospecific synthesis of it or its analogues would be useful. The approach began with piperonal (**134**) as shown in Scheme 39. This aldehyde reacts with the Horner-Emmons reagent **135** to give the cinnamate ester **136** in 99% yield. Basic hydrolysis under phase transfer conditions produces the corresponding carboxylic acid **137** in 84% yield. Treatment with thionyl chloride forms the acid chloride **138**, and this reacts *in situ* with the sodium salt of camphorsultam **115** to generate **139** in 60 % yield. However, no reaction of **139** could be observed in the presence of **84** and lead tetraacetate. This is probably due to a combination of a sterically hindered alkene and the C-2 methyl group, which may prevent the α,β-unsaturated amide from assuming the s-cis conformation. This effect is similar to that seen with **125**. Unfortunately this methodology appears to be unsuitable for preparation of carbidopa.



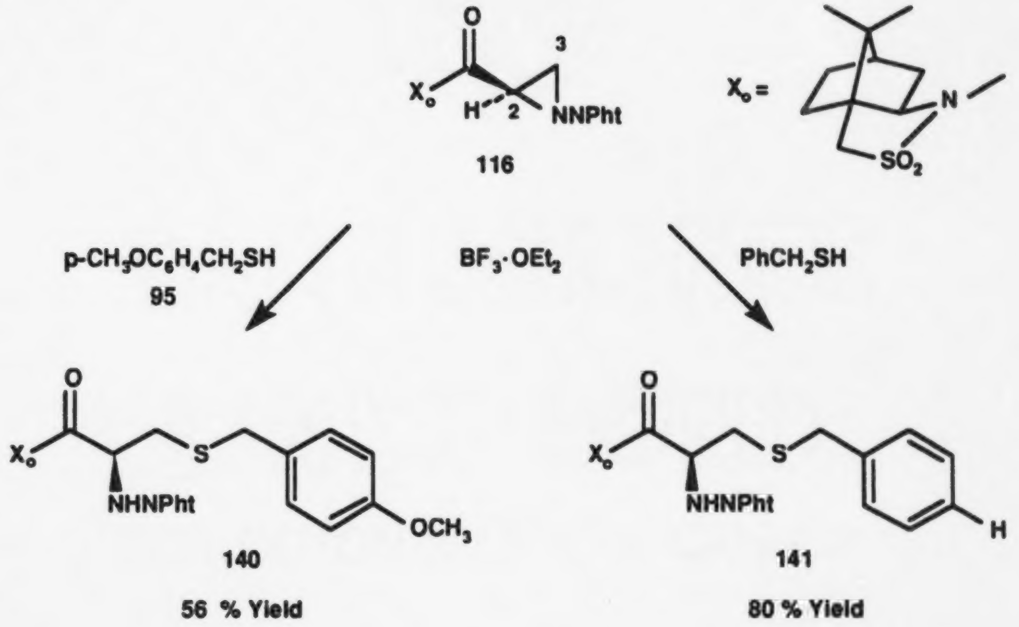
Carbidopa
133

Scheme 39


134
135
99 %
136
NaOH
(CH$_3$)$_4$NOH
84 %
137
SOCl$_2$
138
NaH
115
60 %
139
Pb(OAc)$_4$
PhtNNH$_2$
133

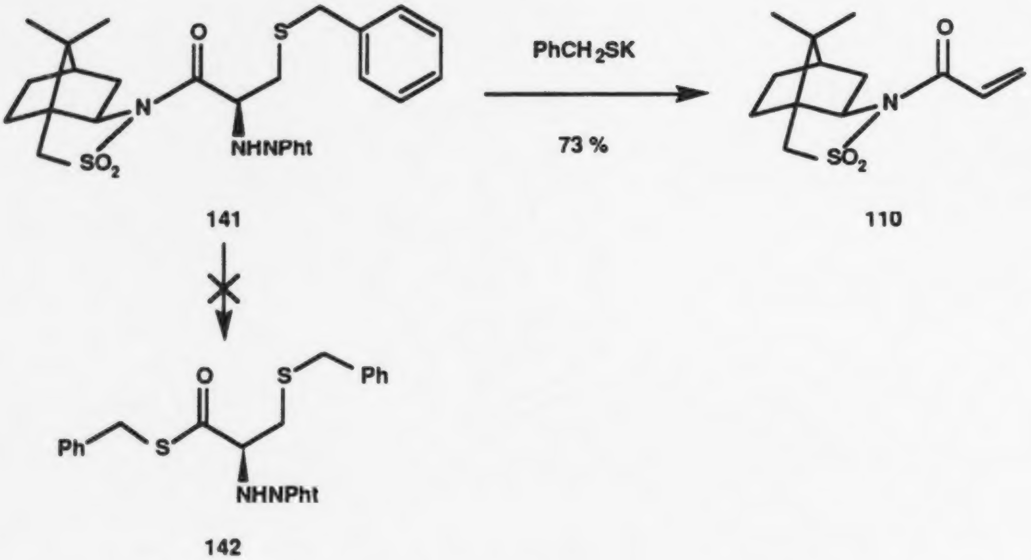
With a route to chiral aziridines available, the next goal was to investigate the aziridine ring opening. *p*-Methoxybenzylthiol (**95**) attacks exclusively at carbon 3 of **116** in dichloromethane using boron trifluoride etherate as Lewis acid catalyst (Scheme 40), to form the hydrazinocysteine derivative **140** in 56 % yield. Compound **116** also reacts with benzyl thiol (**27**) under identical conditions to give **141** in 80 % yield. Surprisingly, none of the hydrazino-isocysteine derivative is observed. The steric bulk of the chiral auxiliary presumably hinders thiol attack at carbon 2.

Scheme 40


O
3
X$_o$
H
2
NNPht
116
X$_o$ =
N
SO$_2$
p-CH$_3$OC$_6$H$_4$CH$_2$SH
95
BF$_3$·OEt$_2$
PhCH$_2$SH
O
X$_o$
S
NHNPht
OCH$_3$
140
56 % Yield
O
X$_o$
S
NHNPht
H
141
80 % Yield

Unfortunately, such hindrance also makes access at the carbonyl group difficult for reagents which could remove the chiral auxiliary. The methods known to remove the Oppolzer chiral auxiliary and retain the carboxylate functionality are: basic aqueous hydrolysis and titanate mediated cleavage.[86, 92] Numerous variations of these procedures[93-99]

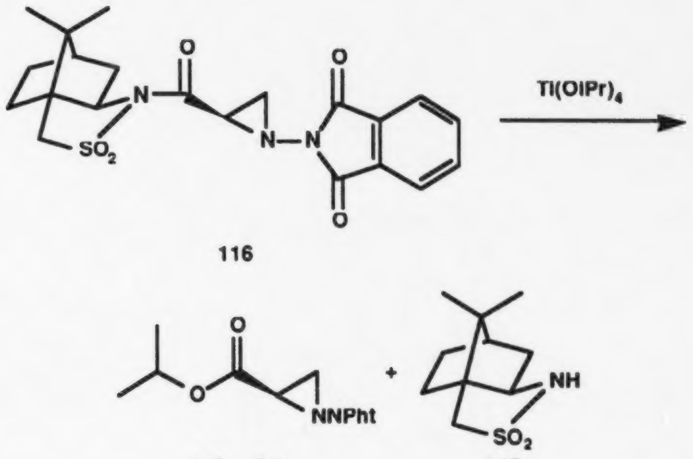
Scheme 41



were attempted but the carbonyl carbon-nitrogen bond could not be successfully cleaved. For example, addition of benzyl thiolate, a strong nucleophile, does not cleave the chiral auxiliary from **141** to give the thioester **142** (Scheme 41).[34] Instead, **110** was isolated in 73 % yield. Attack at sulfur may occur with concomitant elimination to generate **110**.

Since the auxiliary could not be cleaved from the hydrazinocysteine derivative **141**, deprotection of the precursor **116** was examined because the aziridine ring system may reduce steric hindrance at the carbonyl carbon. The aziridine **116** reacts with titanium isopropoxide in THF to form **143** in 3 % isolated yield (Scheme 42). Surprisingly, separation of **143** from the camphorsultam **115** byproduct was very difficult and required HPLC on a normal phase silica gel column.

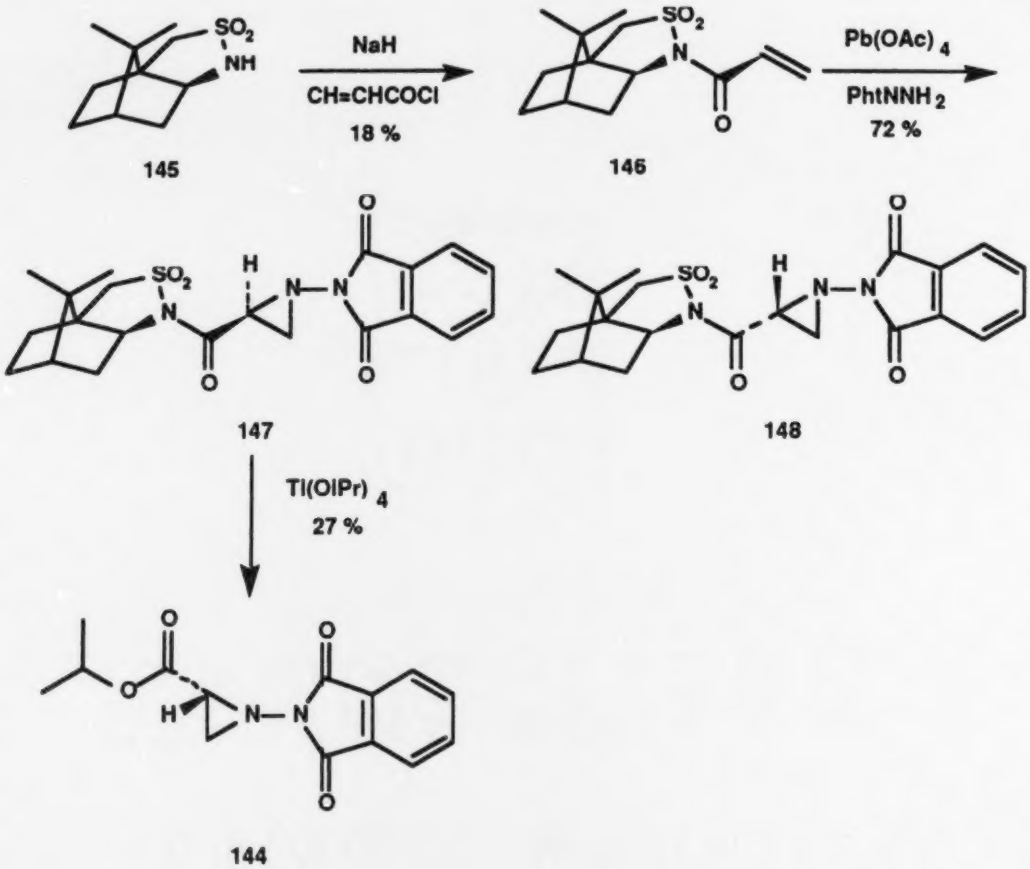
Scheme 42



To determine whether the esterification occurs without epimerization, the enantiomer of **143**, compound **144**, was prepared analogously from **145** (Scheme 43) via the intermediates **146** and **147**. The diastereomer **148** was separated from **147** before the titanium isopropoxide cleavage.

The 200 MHz ^{1}H NMR spectra of **143** shows that two diastereomeric forms are present due to the slow rate of inversion at the aziridine nitrogen (Figure 5).[61] Signals *a,b* and *c,d* result from the methyl groups in the major and minor conformers, respectively. Addition of a 5 mol % solution of the chiral shift reagent europium (III) tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato (Eu(HFC)$_3$) forms diastereomeric complexes with the two invertomers of **143** which gives four sets of signals for the different methyl groups (*a*, δ 1.7 ppm; *b*, δ 1.5; *c,d* δ 1.25) (Figure 6). The ^{1}H NMR spectrum of a 2:1 mixture of the enantiomers **144**:**143** in the presence of 48 mol % Eu(HFC)$_3$ shows

Scheme 43


SO2
NH
145
NaH
CH=CHCOCl
18 %
SO2
N
O
146
Pb(OAc) 4
PhtNNH 2
72 %
SO2
N
O
H
N—N
O
O
147
SO2
N
O
H
N—N
O
O
148
Ti(OiPr) 4
27 %
O
O
H
N—N
O
O
144

appearance of additional resonances (*b, f*) corresponding to one methyl group of each of the enantiomers. These two signals have a relative intensity of 2:1 (Figure 7). Resonances *a, c-e, g* and *h* are due to the remaining unresolved methyl groups. The results indicate that little if any epimerization occurs during titanate mediated ester formation.

Figure 5. Partial ^{1}H NMR spectrum of 143

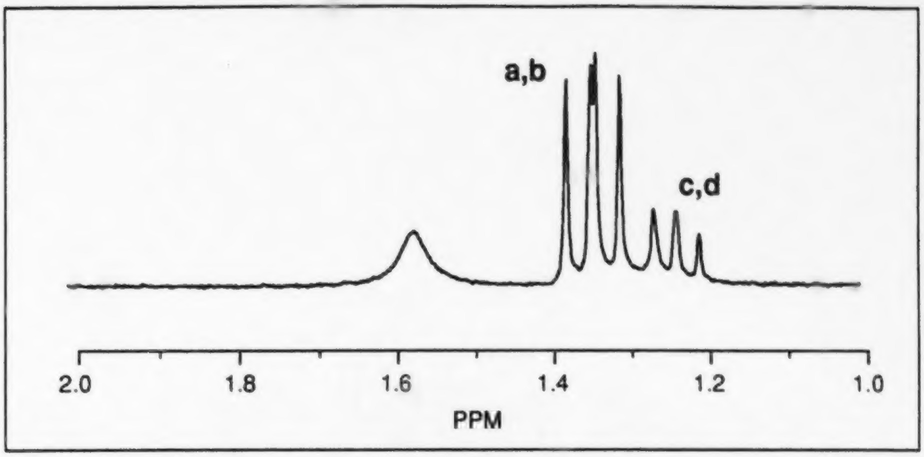


Figure 6. Partial ^{1}H NMR spectrum of 143 and CSR Eu(HFC)$_3$

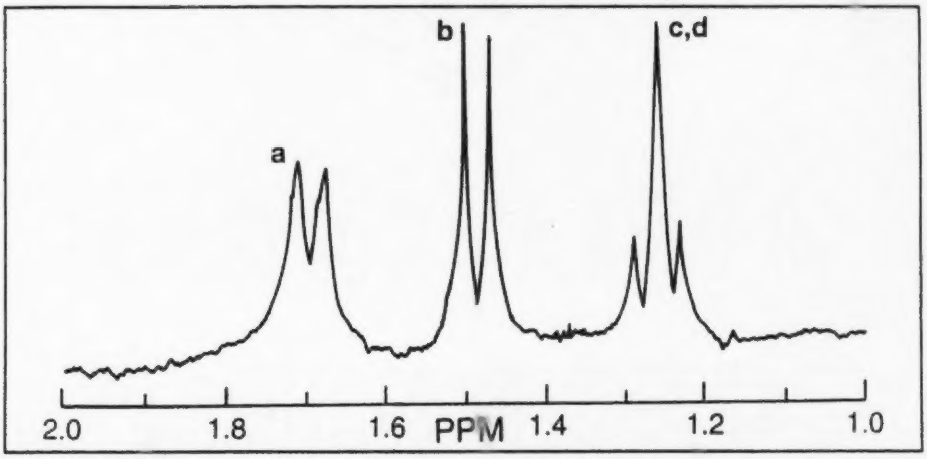
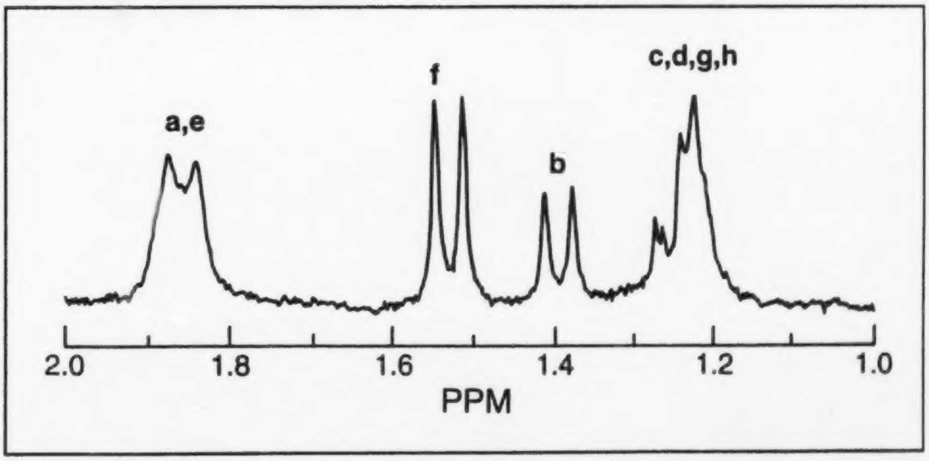
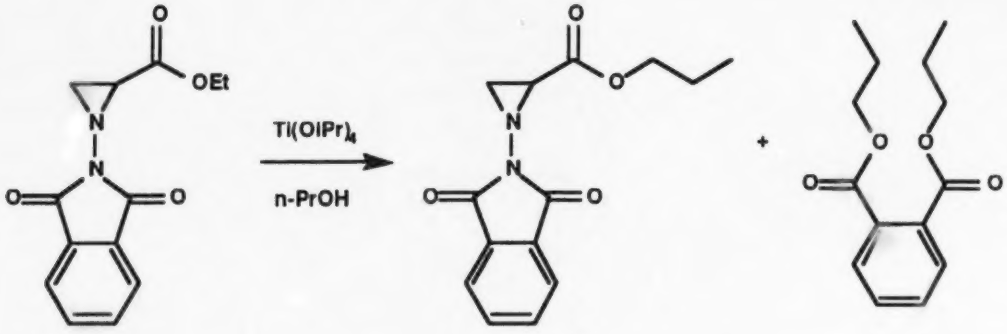


Figure 7. Partial ^{1}H NMR spectrum of 143, 144 and CSR Eu(HFC)$_3$



Attempts to prepare ethyl and methyl esters by the titanate cleavage method were unsuccessful. Interestingly, use of 1-propanol as solvent during titanate cleavage of ethyl ester **94** produces *n*-propyl *N*-phthalimidoaziridine-2-carboxylate (**149**) in 46 % yield and di-*n*-propylphthalate (**150**) in 28 % yield (Scheme 44). This result indicates that hydrolysis of amide bonds is a possible side reaction with titanium isopropoxide.

Scheme 44

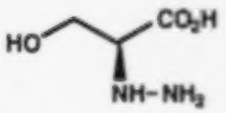


88 **149** 46 % **150** 28 %

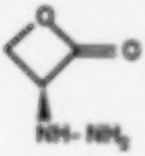
This study shows that aziridination reactions using acrylamides, *N*-aminophthalimide and lead tetraacetate often proceed in good yield (61-94 %) with high diastereoselectivity using the Oppolzer chiral sultam auxiliary. The products open in the desired fashion with sulfur nucleophiles like benzylthiol, but unfortunately useful conditions to cleave the auxiliary from the ring opened products could not be found. In order to generate free chiral α-hydrazinocysteine by this method, an alternative chiral auxiliary will have to be found.

4. Hydrazinoserine

The final target of this work is hydrazinoserine (**151**). This unknown compound promises to be an interesting tool for biological research. Its conversion to *N*-protected derivatives of hydrazinoserine-β-lactone (**152**) and nucleophilic ring opening could allow synthesis of a large number of novel and biologically active hydrazino acids unavailable by



(S)-Hydrazinoserine
151

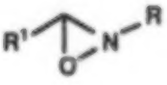


152

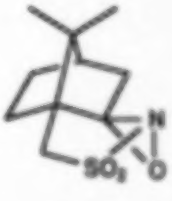
other methods. Two routes to hydrazinoserine (**151**) were examined. The first route relies on amination of an enantiomerically pure serine derivative using an oxaziridine.[54] The second route involves conversion of an enantiomerically pure glycerate ester to a hydrazine derivative by nucleophilic displacement via an activated intermediate.[100]

4.1 Oxaziridine method

Oxaziridines can transfer either heteroatom to attacking nucleophiles depending on the substituent on the nitrogen atom.[101] For example, Davis' reagent, the camphorsulfonyl oxaziridine **153**, oxidizes sulfides to sulfoxides and enolates to α-hydroxyketones.[99] Conversely, *N*-acyl oxaziridines such as **154** tend to transfer the nitrogen and its substituent.[102]

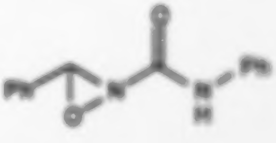


An Oxaziridine



153

Oxidizing Agent

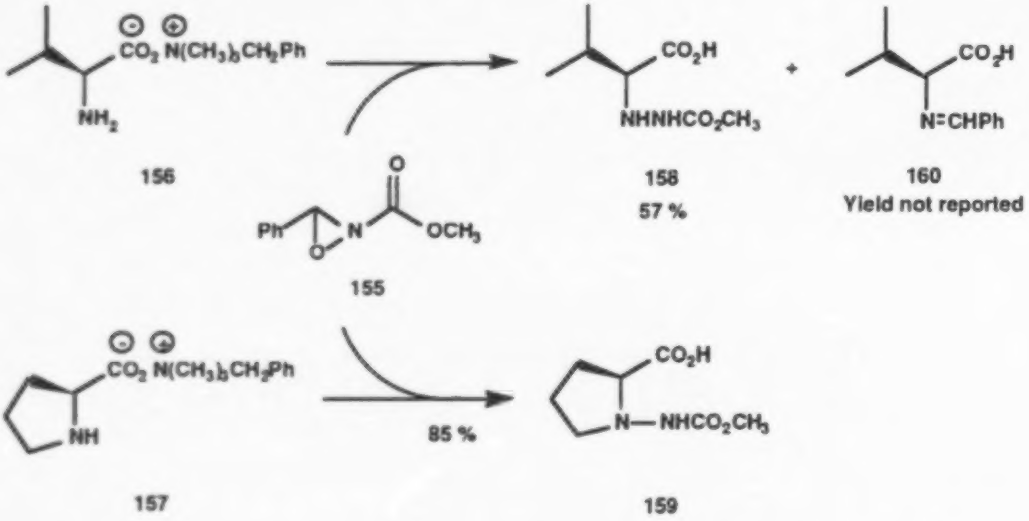


154

Aminating Agent

Recently, Collet and co-workers have shown that 1-methoxycarbonyl-3-phenyloxaziridine (**155**) reacts with amine nucleophiles with transfer of the oxaziridine ring nitrogen.[54] For example, the benzyltrimethyl ammonium salts of the amino acids valine (**156**) and proline (**157**) react with **155** to give **158** and **159** in 57 % and 85 % yields, respectively (Scheme 45). The mechanism is thought to involve nucleophilic attack at the ring nitrogen with N-O bond cleavage. Subsequent expulsion of benzaldehyde results in the hydrazino acid derivatives plus, in the case of valine, the imine **160** (yield not reported) produced by condensation of benzaldehyde with unreacted starting material. Only these two hydrazino acid derivatives with relatively durable side chains were reported. We decided to investigate the generality of this procedure by using an amino acid with a more sensitive substituent (e.g. hydroxyl, thiol). This oxaziridination route is attractive because the hydrazino acid skeleton can be assembled in relatively few steps under mild conditions.

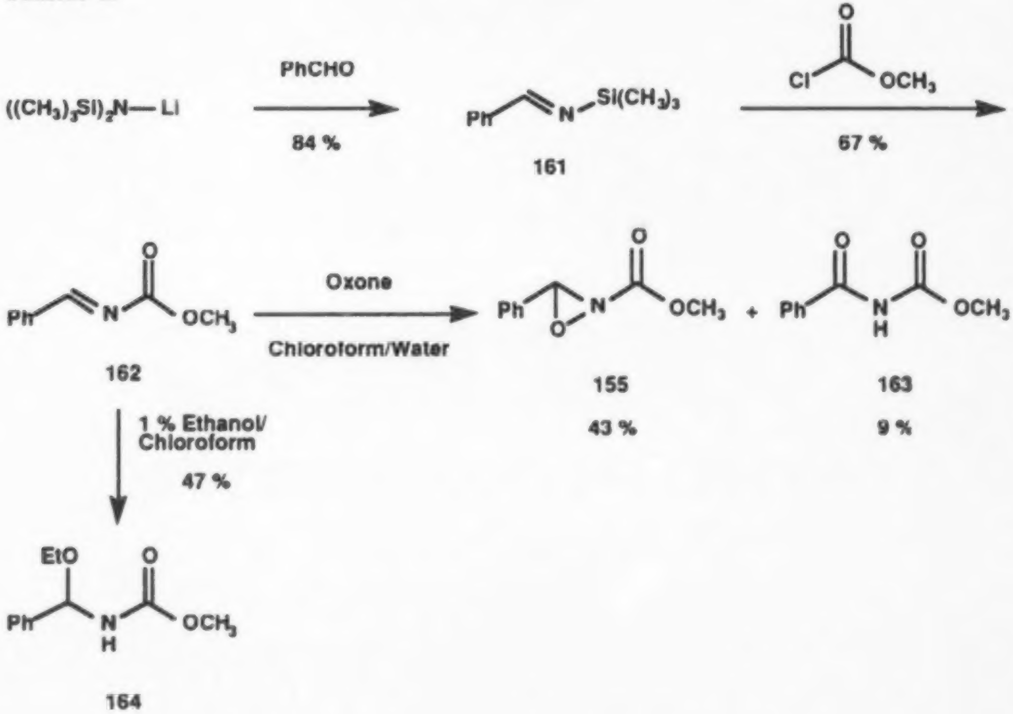
Scheme 45


$CO_2^{\ominus}\ \overset{\oplus}{N}(CH_3)_3CH_2Ph$
NH_2
156
CO_2H
$NHNHCO_2CH_3$
158
57 %
+
CO_2H
N=CHPh
160
Yield not reported
O
Ph
N
O
OCH_3
155
$CO_2^{\ominus}\ \overset{\oplus}{N}(CH_3)_3CH_2Ph$
NH
157
85 %
CO_2H
$N—NHCO_2CH_3$
159

1-Methoxycarbonyl-3-phenyloxaziridine (**155**) was prepared by the literature procedure (Scheme 46).[54] Thus, lithium hexamethyldisilazide reacts with benzaldehyde to give the *N*-silylimine **161** in 84 % yield. Condensation with methyl chloroformate generates *N*-methoxycarbonylbenzaldimine (**162**) in 67 % yield. Oxidation of **162** using oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, potassium peroxymonosulfate) gives an easily separable mixture of the desired reagent **155** and the rearrangement product, methoxycarbonylbenzamide (**163**) in 43 % and 9 % yields, respectively (overall: 24 % yield, literature yield 39 %).[54] The last step employs a two phase system of water and chloroform. It is vital that the ethanol used to stabilize the chloroform is removed prior to use. If this is not done ethanol adds to the *N*-acylimine **162** to form **164** in 47 % yield.

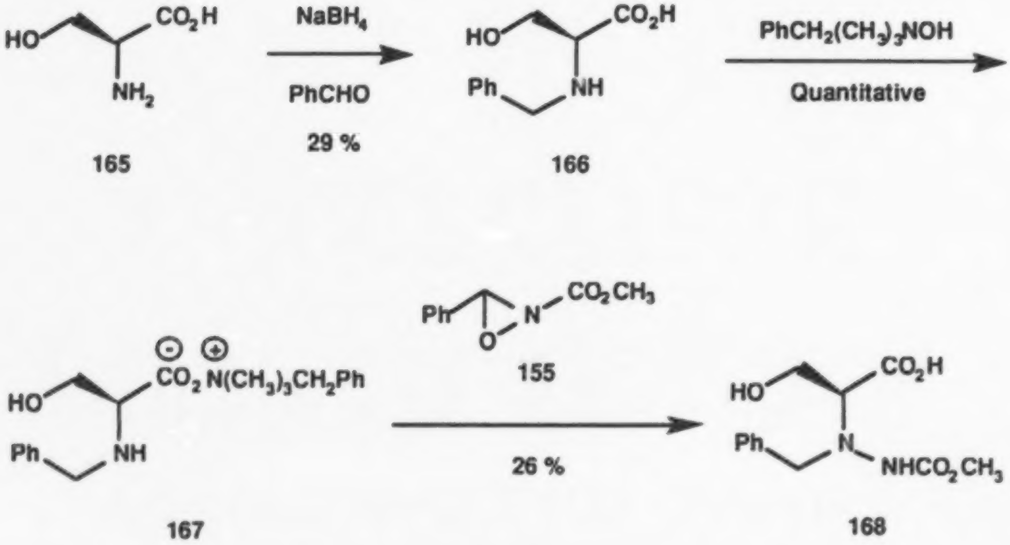
Since the amination procedure requires reaction between a water soluble amino acid and a lipophilic reagent **155**, a tetraalkylammonium salt of *N*-benzylserine was prepared

Scheme 46


((CH$_3$)$_3$Si)$_2$N—Li
PhCHO
84 %
Ph
N
Si(CH$_3$)$_3$
161
O
Cl
OCH$_3$
67 %
Ph
N
O
OCH$_3$
162
Oxone
Chloroform/Water
Ph
N
O
O
OCH$_3$
155
43 %
+
Ph
O
N
H
O
OCH$_3$
163
9 %
1 % Ethanol/
Chloroform
47 %
EtO
O
Ph
N
H
OCH$_3$
164

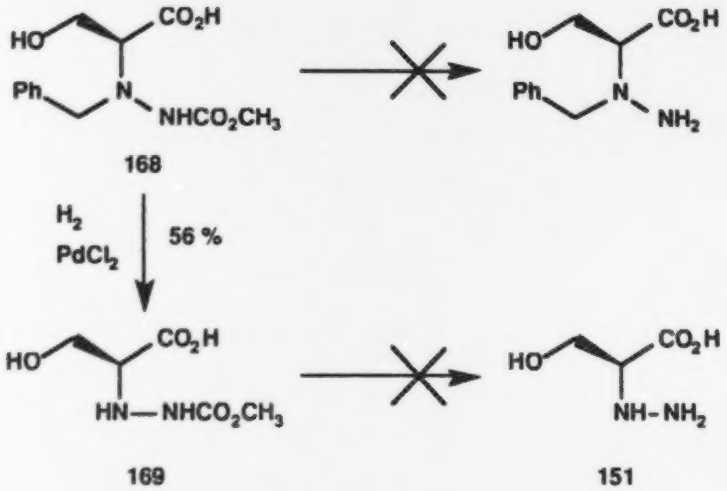
to enhance the likelihood of successful transformation. The use of the *N*-benzyl group should also suppress the undesired side reaction (e.g. formation of **160**). As shown in Scheme 47, (*S*)-serine (**165**) reacts with benzaldehyde in NaOH solution containing sodium borohydride to give *N*-benzylserine (**166**) in 29 % yield (literature yield 35 %).[103] Addition of benzyltrimethylammonium hydroxide transforms this material to benzyltrimethylammonium salt **167** in near quantitiative yield.[95] The purified oxaziridine **155** aminates **167** in dichloromethane solution at 0 °C to form the previously unknown (2*S*)-N_α-benzyl-N_β-(methoxycarbonyl)hydrazinoserine (**168**) in 26 % yield.

Scheme 47


HO
CO₂H
NH₂
165
NaBH₄
PhCHO
29 %
HO
CO₂H
Ph
NH
166
PhCH₂(CH₃)₃NOH
Quantitative
Ph
N
CO₂CH₃
O
155
HO
CO₂ N(CH₃)₃CH₂Ph
Ph
NH
167
26 %
HO
CO₂H
Ph
N
NHCO₂CH₃
168

Several procedures are available to remove methoxycarbonyl protective groups from amines.[36] However, hydrazino acids are inherently unstable to basic conditions, which limits the possible procedure to neutral or acidic methods, such as halogen acids or iodotrimethylsilane. All efforts to develop methodology for the removal of the methoxycarbonyl group from **168** were unsuccessful (Scheme 48), because the

Scheme 48

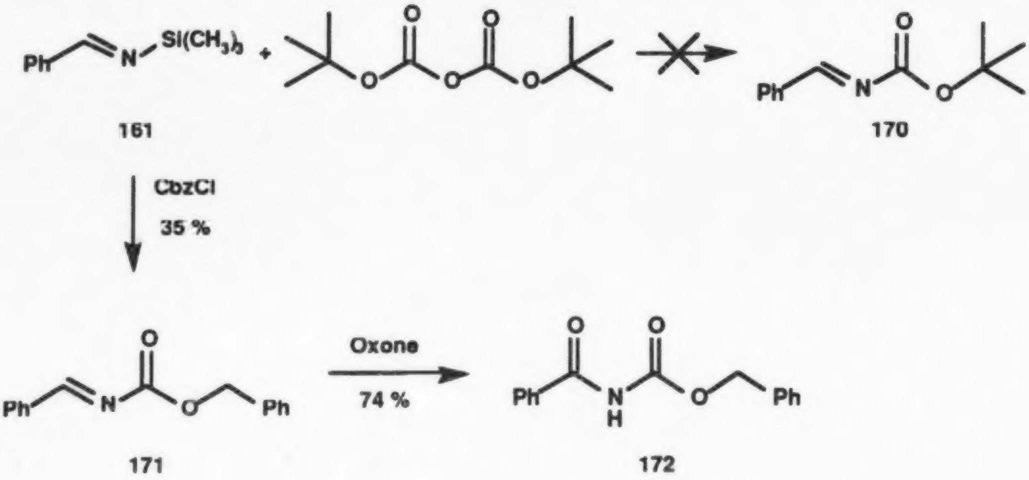


compound decomposes rapidly upon exposure to the harsh conditions required for carboxymethyl group cleavage.

In contrast, reductive removal of the benzyl group of **168** occurs readily with $PdCl_2$ in methanol to give **169** in 56 % yield. Unfortunately, all attempts to remove the methoxycarbonyl group of **169** with standard reagents gave complex mixtures.[104, 105] Enzymatic cleavage with carboxypeptidase W was also tried but **169** was not hydrolysed. Final removal of the methoxycarbonyl protective group remains the obstacle to forming hydrazinoserine by this route.

To overcome this problem, the possibility of using other groups in the oxaziridine reagent was investigated in collaboration with Dr. Daniel Niederer of our research group. One common amine protective group for amino acid synthesis is the *t*-butyloxycarbonyl (*t*-BOC) group, which can be easily removed under acid conditions. The *N*-silylimine **161** was added to a solution of *t*-BOC anhydride (Scheme 49) but no formation of **170** could be observed, presumably because steric bulk hinders the reaction.

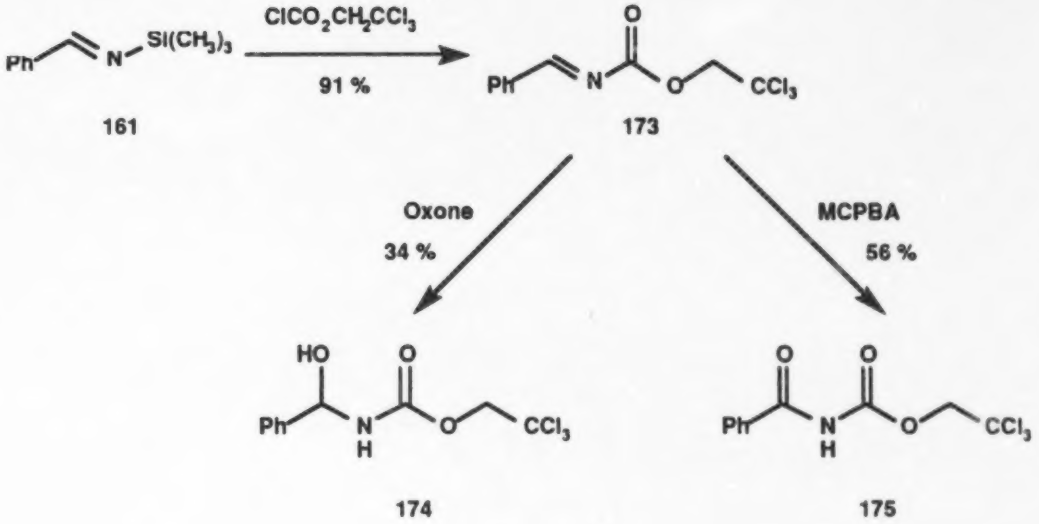
Scheme 49



Another common amine protective group is the benzyloxycarbonyl (Cbz) group, which is most often removed by hydrogenolysis but other procedures are available.[95] Cbz chloride reacts with **161** to give the *N*-acylimine **171** in 35 % yield (Scheme 49). However, **171** reacts with oxone® to give benzyloxycarbonylbenzamide (**172**) in 74 % yield.

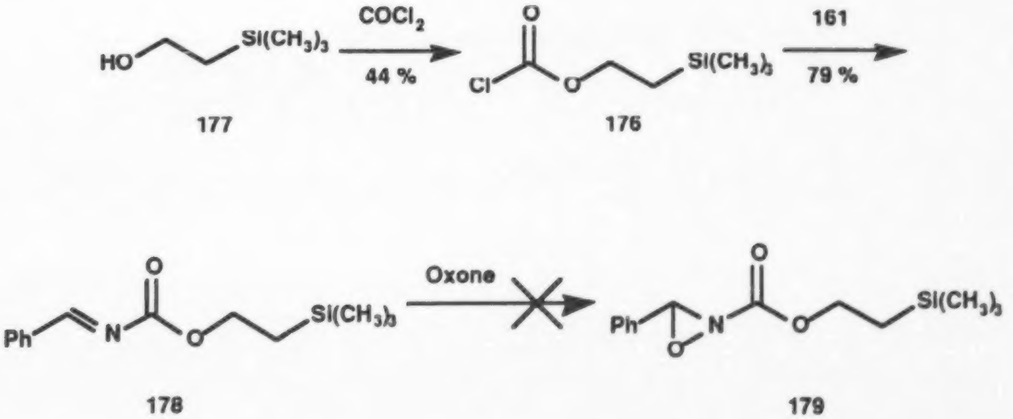
The trichloroethoxycarbonyl group can be removed by zinc under acidic conditions. Compound **161** reacts with 2,2,2-trichloroethoxycarbonyl chloride to give the benzaldimine **173** in 91 % yield (Scheme 50). Oxidation of **173** using oxone® gives the hydrated product **174** in 34 % yield. Apparently, the aqueous phase reacts with **173** faster than the oxone can, resulting in addition of water. Because *m*-chloroperbenzoic acid (MCPBA) is a versatile oxidizing agent soluble in organic solvents, the oxidation of **173** was attempted in the absence of the aqueous phase. Unfortunately, **173** reacts with MCPBA to give [(2,2,2-trichloroethoxy)carbonyl]benzamide **175** in 56 % yield (Scheme 50).

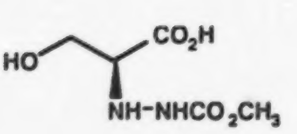
Scheme 50


ClCO$_2$CH$_2$CCl$_3$
91 %
161
173
Oxone
34 %
MCPBA
56 %
174
175

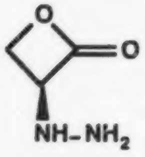
The final protective group investigated was the 2-trimethylsilylethoxycarbonyl group which can be removed by fluoride ion. The chloroformate **176** is readily prepared from 2-trimethylsilylethanol (**177**) and phosgene in 44 % yield (Scheme 51). Compound

Scheme 51


COCl$_2$
44 %
161
79 %
177
176
Oxone
178
179



169



152

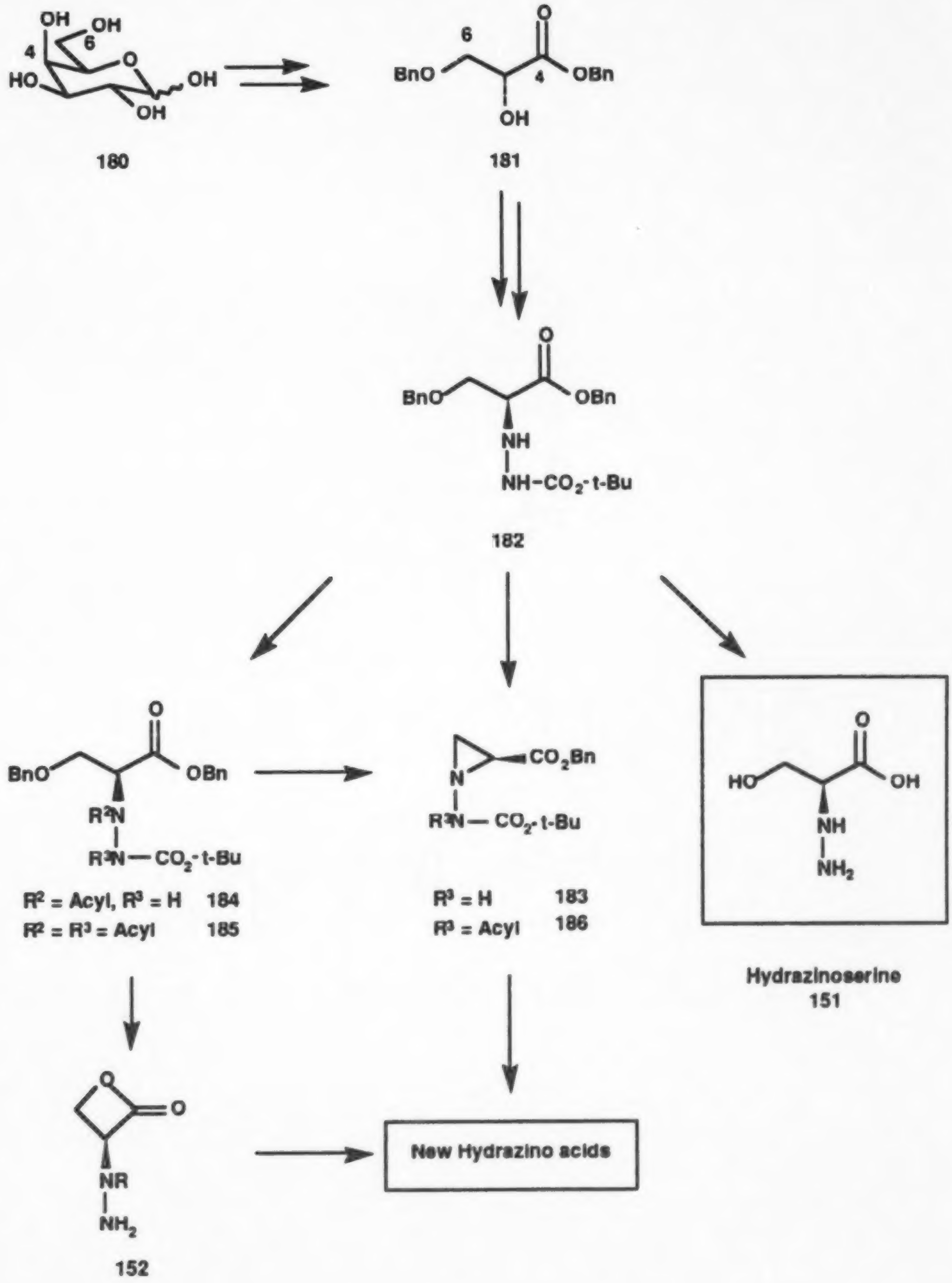
176 reacts with **161** to give the expected imine **178** in 79 % yield. The oxidations of **178** have not produced oxaziridine **179** to date.

Although **151** could not be prepared by this methodology, a number of potential protective groups for oxaziridines were studied. In addition, previously unreported *N*β-protected hydrazinoserine **169** has been synthesized, and promises to be a useful starting point for formation of derivatives of hydrazinoserine β-lactone (**152**).

4.2 Glycerate method

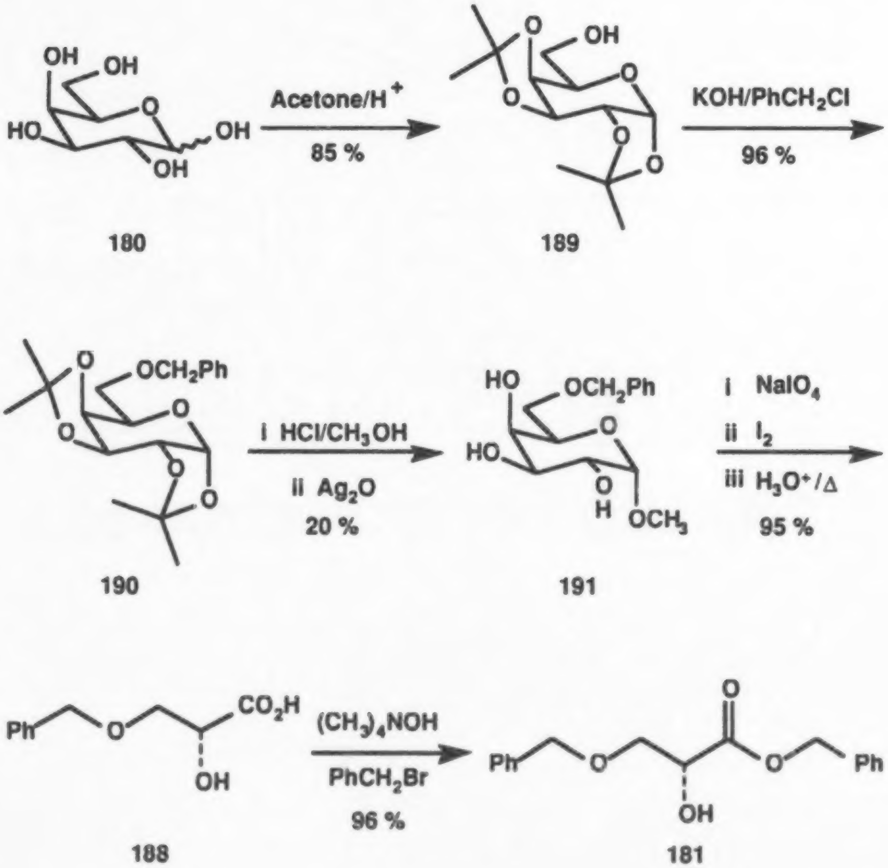
Another potential route to novel hydrazino acids consists of converting galactose (**180**) to the 1,3-diprotected glycerate **181** (Scheme 52).[100] In addition to hydrazinoserine **151**, which is the primary goal of this study, it may be possible to form *N*-protected aminoaziridines **183** employing a procedure similar to the method of Okawa and Nakajima.[23, 28, 79] Also, it should be possible to protect one or both of the nitrogens of **182** to afford access to compounds such as **184** or **185**, respectively. Each of these may in turn lead to protected aziridines **186** or protected hydrazinoserine-β-lactones **187**, and thereby to hydrazino acids.

Scheme 52


OH
OH
6
4
O
HO
OH
OH
180
O
6
BnO
4
OBn
OH
181
O
BnO
OBn
NH
NH-CO2-t-Bu
182
O
BnO
OBn
R2N
R3N — CO2-t-Bu
R2 = Acyl, R3 = H 184
R2 = R3 = Acyl 185
N
CO2Bn
R3N — CO2-t-Bu
R3 = H 183
R3 = Acyl 186
O
HO
OH
NH
NH2
Hydrazinoserine
151
O
O
NR
NH2
152
New Hydrazino acids

In 1954, Ballou and Fischer reported the degradation of (+)-galactose **180** into 3-*O*-benzylglyceric acid **188** (Scheme 53).[100] Since then, **188** has been used for the preparation of many enantiomerically pure compounds.[106, 107] (+)-Galactose (**180**) reacts with acetone and sulfuric acid to give galactose diacetonide **189** in 85 % yield (Scheme 53). Benzylation using benzyl chloride and powdered potassium hydroxide produces **190** in 96 % yield. This compound **190** reacts with HCl in methanol to cleave the acetonide groups and concomitantly form the methyl galactoside **191** in 20 % yield. The one pot oxidation to the dialdehyde with $NaIO_4$, further oxidation to the dicarboxylic acid with I_2, and aqueous acidic hydrolysis gives 3-*O*-benzylglyceric acid (**188**) in 95 % yield. The tetramethyl ammonium salt of **188** reacts with benzyl bromide under Wagenknecht

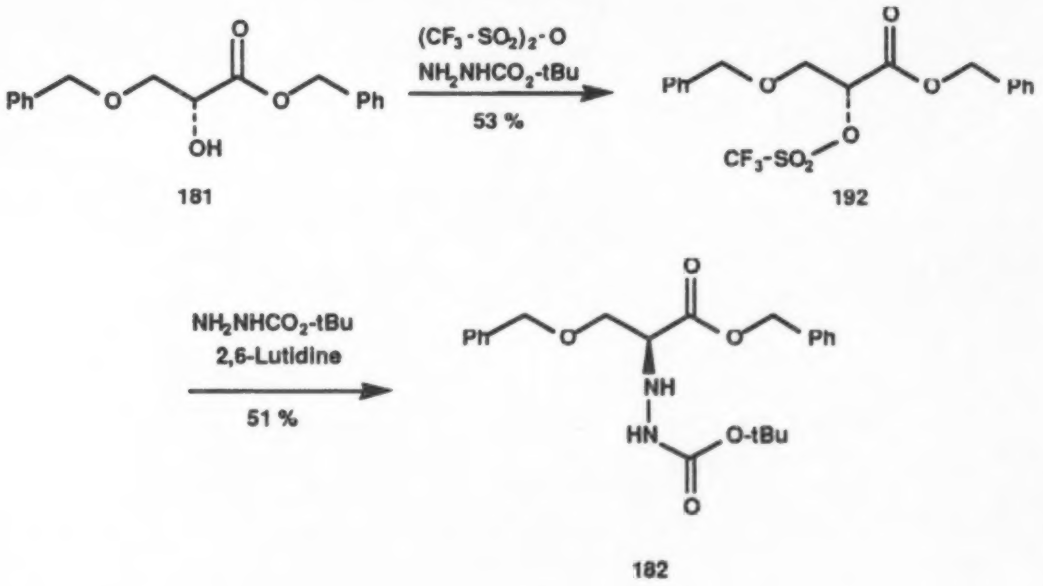
Scheme 53


OH
OH
HO
O
OH
OH
180
Acetone/H+
85 %
O
OH
O
O
O
O
189
KOH/PhCH2Cl
96 %
O
OCH2Ph
O
O
O
O
190
i HCl/CH3OH
ii Ag2O
20 %
HO
OCH2Ph
O
HO
O
H
OCH3
191
i NaIO4
ii I2
iii H3O+/Δ
95 %
Ph
O
CO2H
OH
188
(CH3)4NOH
PhCH2Br
96 %
O
Ph
O
O
Ph
OH
181

conditions[106, 108] to give **181** in 96 % yield.

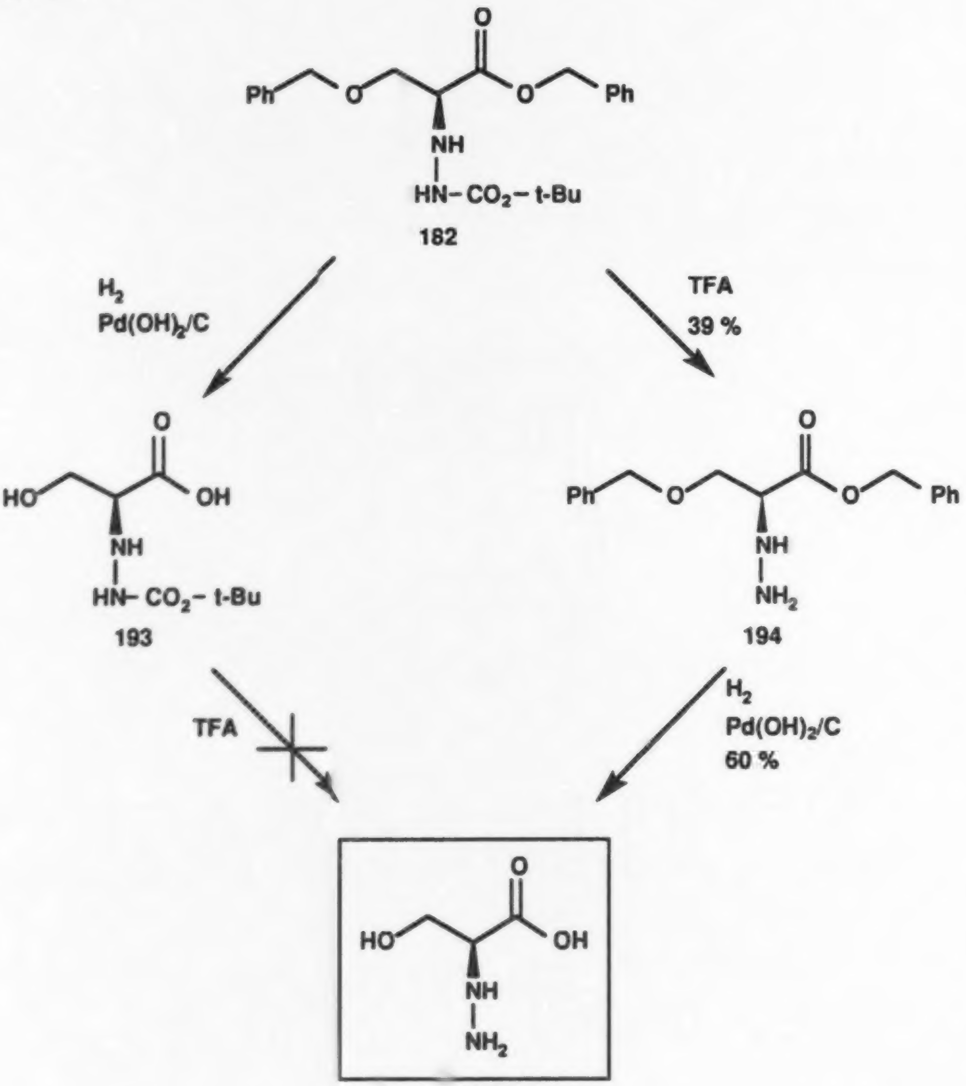
Compound **182** was first prepared by Dr. Evon Bolessa of our group. Thus, trifluoromethyl sulfonic anhydride (triflic anhydride) reacts with the alcohol **181** to generate the sulfonate **192** (Scheme 54).[107] Addition of *t*-butylcarbazate **76** in the presence of two equivalents of 2,6-lutidine forms the hydrazino acid derivative **182** in 51 % yield.

Scheme 54


Ph
O
O
O
Ph
OH
181
$(CF_3\cdot SO_2)_2\cdot O$
NH_2NHCO_2-tBu
53 %
Ph
O
O
O
Ph
O
CF_3-SO_2
192
NH_2NHCO_2-tBu
2,6-Lutidine
51 %
Ph
O
O
O
Ph
NH
HN
O-tBu
O
182

For the preparation of hydrazinoserine (**151**), the protective groups had to be removed. Compound **182** reacts with hydrogen in the presence of 3 % palladium hydroxide on carbon[109] to give the debenzylated compound **193** (Scheme 55). The material was unstable, therefore removal of the *t*-BOC group was attempted with the crude material. Unfortunately, reaction with TFA gives a complex mixture, and none of the expected hydrazinoserine (**151**) could be detected. However, the dibenzyl compound **182** readily reacts with TFA to form the free hydrazino compound **194** which can be

Scheme 55



isolated as the monohydrociloride salt in 39 % yield. Hydrogenation of **194** using $Pd(OH)_2$ on carbon catalyst gves the desired hydrazinoserine (**151**) in 60 % yield.

To confirm that the dsplacement reaction of **192** with **76** occurs with complete inversion of the configurationat C-2, an assay to determine the presence of both isomers was required. Marfey has used N_{α}-(2,4-dinitro-5-fluorophenyl)-(*S*)-alaninamide (**195**) to form diastereomers of several racemic amino acids,[110] and various techniques are available for the separation of such diastereomers.[111-113] In a model system, (*RS*)-serine **196**, reacts with N_α-(2,4-dinitro-5-fluorophenyl)-(*S*)-alaninamide **195** to give a mixture of the diastereomers **197** and **198** (Scheme 56). These two compounds separate readily by

Scheme 56

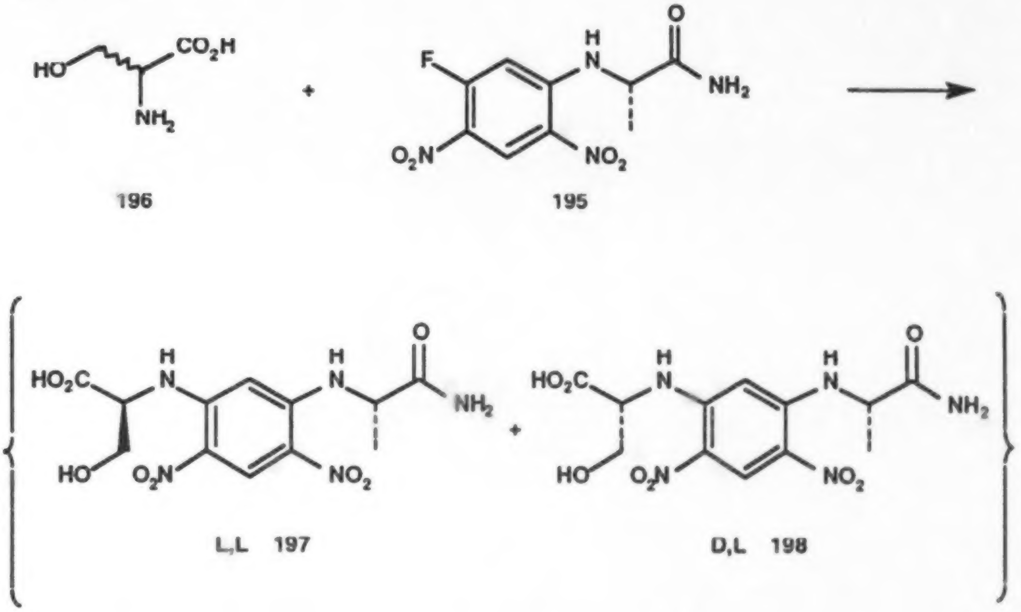
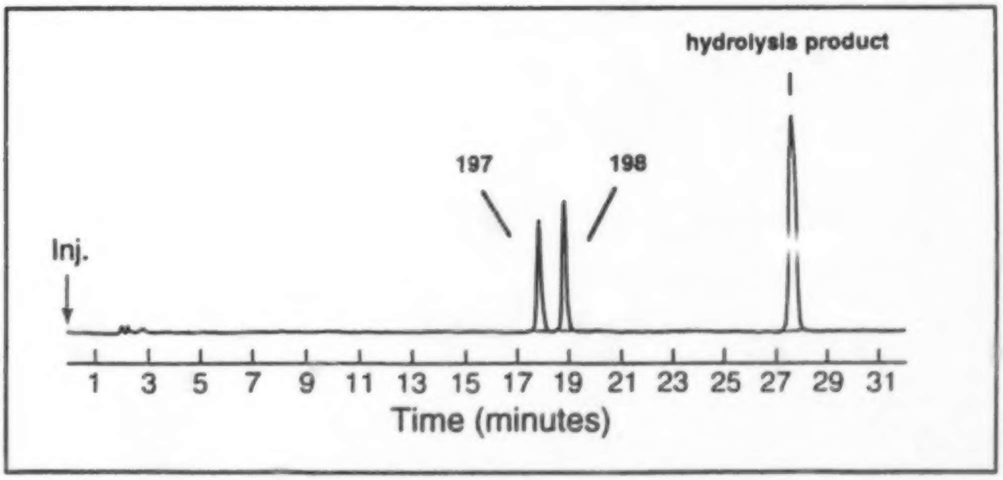
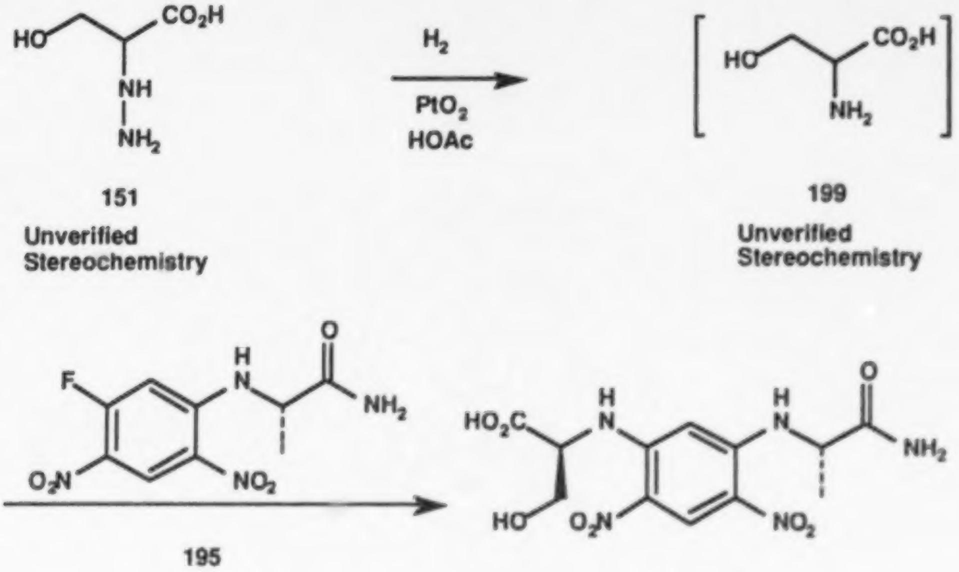

HO
CO₂H
NH₂
196
+
F
H
N
O
NH₂
O₂N
NO₂
195
HO₂C
H
N
H
N
O
NH₂
HO
O₂N
NO₂
L,L 197
+
HO₂C
H
N
H
N
O
NH₂
HO
O₂N
NO₂
D,L 198

Figure 8. HPLC of 197 and 198.



reversed phase HPLC as shown in Figure 8. This assay allows analysis of the hydrazinoserine (**151**) for enantiomeric excess. Thus, **151** reacts with hydrogen in the presence of platinum oxide and a trace of acid to give serine (**199**) (Scheme 57).[114] The serine **199**

Scheme 57


HO
CO$_2$H
NH
NH$_2$
H$_2$
PtO$_2$
HOAc
HO
CO$_2$H
NH$_2$
F
H
N
O
NH$_2$
O$_2$N
NO$_2$
HO$_2$C
H
N
H
N
O
NH$_2$
HO
O$_2$N
NO$_2$

151
Unverified
Stereochemistry

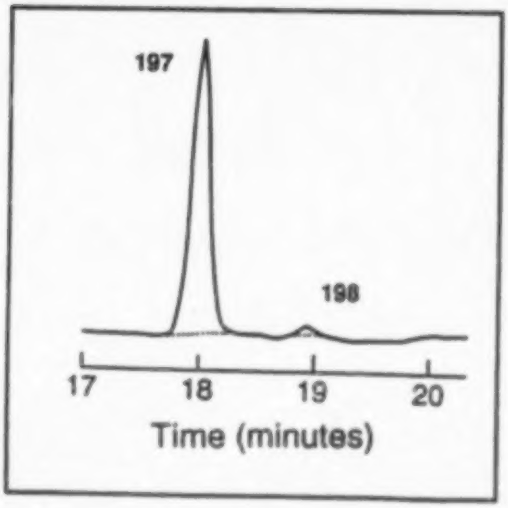
199
Unverified
Stereochemistry

195

L,L **200**

Minimum ratio
98:2 This isomer

Figure 9. HPLC of hydrazinoserine derivative 200



condenses with the Marfey reagent **195** to give **200**, which could in principle consist of a mixture of **197** and **198**. HPLC analysis of **200** with the same conditions as before demonstrates that the peak areas of the first eluting compound **197** to the second **198** are in the ratio of a minimum 98:2 (Figure 9). Thus, the nucleophilic displacement (**193**-**182**) proceeds with complete inversion of configuration and the hydrazinoserine has a minimum 96 ± 4 % e.e. The overall yield from galactose is 3.5 % over 7 steps.

In conclusion, several novel synthetic intermediates have been prepared which display the potential to be valuable for the synthesis of novel amino and hydrazino acids. In particular, synthesis of optically pure hydrazinoserine (**151**) has provided a key potential inhibitor for a host of pyridoxal phosphate enzymes which utilize serine. In addition, the availability of this compound permits exploration of routes to its β-lactone and thus to other chiral α-hydrazino acids bearing sensitive β-substituents.

EXPERIMENTAL

General.

All reactions requiring anhydrous conditions or involved air-sensitive reagents were done under slight positive pressure of dry Ar. Dry reactions were performed using oven-dried glassware (>6 h at 140 °C) which was cooled under Ar. The term *in vacuo* refers to the removal of solvent on a rotary evaporator to constant sample weight. Dry solvents were prepared under an Ar atmosphere according to Perrin *et al.*:[115] benzene, toluene, tetrahydrofuran (THF) and dioxane were distilled from sodium/benzophenone; acetonitrile, diisopropylamine, pyridine and dichloromethane were distilled from calcium hydride; methanol and ethanol were distilled from magnesium/catalytic iodine; dry dimethylformamide was purchased from Aldrich Chemical Co. Ethyl ether was obtained and used as anhydrous reagent except for the chromatography of compound **108** for which the ether was freshly passed through a column of dry neutral alumina (80 g $Al_2(O)_3$ per 700 mL ether).[115] Water was Milli Q quality.

All reagents were ACS grade or finer. All commercial organometallic reagents were obtained from Aldrich Chemical Co. Butyl lithium (BuLi) was titrated immediately before use against menthol/phenanthroline.[116]

Cation exchange resins were BioRad AG50W-X8 (H^+ form, 50-100 and 200-400 mesh) and Amberlyst XN-1010 (H^+ form). Anion exchange resin was BioRad AG1W-X8 (Cl^- form, 50-100 mesh). Ion retardation resin was BioRad AG11W-X8 (Self Absorbed, 50-100 mesh).

Whenever possible the progress of reactions was monitored by thin-layer chromatography (TLC) using one or more of the following for visualization: UV absorption by fluorescence quenching; iodine staining; dodecaphosphomolybdic acid spray for reducing compounds; bromocresol green spray for acids; ninhydrin spray for amino acids and amines. All spray reagents were prepared and used as described by Krebs *et al.*[117] Commercial TLC plates were silica, Merck 60F-254, or reverse-phase, Merck

RP-$8F_{254}S$, or Merck RP-$18F_{254}S$. Silica gel for column chromatography was Merck type 60, 70-230 mesh. Flash chromatography was executed according to Still *et al.*[118] using Merck type 60, 230-420 mesh silica gel. Normal phase medium pressure liquid chromatography (MPLC) employed a column of Merck Kieselgel 60H (50 g, 2.5 X 30 cm). Reverse-phase MPLC was performed on a Merck Lobar Lichroprep RP-8 column (Size B). All solvent mixtures are listed as volume ratios (v/v). High performance liquid chromatography (HPLC) was performed on either a Hewlett Packard 1082B liquid chromatograph equipped with a variable wavelength UV detector or a Biorad HPLC, UV monitor model 1305A, and Gradient Module. HPLC columns were Waters micro bondapak, SiO_2, RP-8 and RP-18.

All literature compounds had ^1H NMR, MS and IR spectra consistent with the assigned structures. The NMR spectra were recorded on Bruker WP80, WH-200, AM-300, WH-360, AM-400 or Varian EM360, Varian Unity 500 MHz instruments using tetramethylsilane (TMS) or deuterated sodium 3-(trimethylsilyl)-1-propanesulfonate (TSP) in D_2O as internal reference standards. IR spectra were recorded on either of NICOLET 7199 or 20SX fourier transform infrared spectrometers. Uncorrected melting points were obtained on a Büchi Melting point apparatus. High resolution mass spectra were recorded with a Kratos A.E.I. MS 50 using an electron impact (EI) source. Chemical ionization (CI) mass spectra were recorded with a Kratos A.E.I. MS12. Fast atom bombardment mass spectra were recorded with a Kratos A.E.I. MS9 using a modified fast atom bombardment (FAB) source and saddle field xenon atom gun. Combustion analyses were determined with Carlo Erba 1108 or Perkin Elmer 240B elemental analyzers. Optical rotations were determined using a Perkin Elmer 241 polarimeter with a microcell (10.00 cm, 0.9 mL) at ambient temperature (25 ± 2°C).

(2*S*,3*R*)-2-[(Phenylsulfonyl)amino]-3-hydroxybutanoic Acid (2)

The literature procedure[37] was followed using the amounts outlined below: To **1** (9.53 g, 80.0 mmol) in H_2O (120 mL) and Na_2CO_3 (25.1 g, 237 mmol) was added $PhSO_2Cl$ (15 mL, 21 g, 120 mmol) and the mixture was stirred for 5 h at 20 °C. The mixture was washed with Et_2O (2 X 50 mL), acidified to pH 2 (6M HCl), and extracted with EtOAc (3 X 50 mL). The extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give the known **2** as a colourless powder (14.4 g, 55.5 mmol, 69 % yield): mp 142-145 °C (lit[37] mp 146-148 °C); IR (KBr disk) 3441, 3298, 2940, 1727 cm^{-1}; ^1H NMR (200 MHz, CD_3COCD_3) δ 7.44-7.93 (m, 5H, ArH), 6.33 (d, 1H, J=9.0 Hz, NH), 4.21 (m, 1H, $CHCH_3$), 3.86 (dd, 1H, J=3.0, 9.4 Hz, CHN), 3.75 (br. s, 1H, COOH), 1.18 (d, 3H, J=6.0 Hz, CH_3); MS (CI, NH_3) 277 (277 calcd. for MNH_4^+).

(3*S*,4*R*)-3-[(Phenylsulfonyl)amino]-4-methyl-2-oxetanone (3)

The literature procedure[35] was followed with the modifications outlined below: To **2** (3.00 g, 11.5 mmol) in pyridine (50 mL) was added *p*-bromobenzenesulfonyl chloride (6.09 g, 23.8 mmol). The mixture was stirred for 30 min at -43 °C, then for 40 min at -10 °C, and then poured onto ice (300 mL). The mixture was acidified to pH 2.5 (6M HCl), and extracted with EtOAc (3 X 100 mL). The extracts were dried with Na_2SO_4 and concentrated *in vacao*. Flash chromatography (hexanes:EtOAc 2:1) gave the known **3** as a colourless powder (1.28 g, 5.31 mmol, 46 % yield): mp 115-117 °C (lit[35] mp 113-114 °C); IR ($CHCl_3$ cast) 3280, 2920, 1169, 1827 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50-8.00 (m, 5H, ArH), 6.14 (br. s, 1H, NH), 5.18 (dd, 1H, J=4.0, 5.0 Hz, CHN), 4.90 (m, 1H, $CHCH_3$), 1.50 (d, 3H, J=3.0 Hz, CH_3); MS (CI, NH_3) 259 (MH^+).

(2*R*,3*S*)-2-[(Phenylsulfonyl)amino]-3-isothioureidobutanoic Acid (4)[35]

To a solution of **3** (105 mg, 0.434 mmol) in CH_3CN (3 mL) was added thiourea (42.8 mg, 0.564 mmol) in CH_3CN (3 mL) and the mixture was warmed to 60 °C for 3 days. The precipitate was filtered to give the known **4** as a colourless solid (70.9 mg, 0.224 mmol, 52 % yield): mp 177-178 °C (lit[35] mp 174-175 °C); IR (KBr disk) 3348, 3000, 1625 cm^{-1}; ^1H NMR (200 MHz, DCl/D_2O) δ 7.60-8.00 (m, 5H, ArH), 4.43 (d, 1H, J=4.0 Hz, CHN), 4.25 (dd, 1H, J=4.0, 7.0 Hz, $CHCH_3$), 1.36 (d, 3H, J=7.0 Hz, CH_3); FAB MS (glycerol/HCl) 318 (MH^+).

(2*R*,3*S*)-2-[Phenylsulfonyl)amino]-3-thiobutanoic Acid (5)[119]

To a solution of **4** (80.5 mg, 0.254 mmol) in degassed H_2O (20 mL) was added NaOH (1M, 0.5 mL, 0.5 mmol) and the mixture was stirred at 20 °C for 2 h. HCl (25 mM, 20 mL) was added, the mixture was extracted with $CHCl_3$ (3 X 40 mL), and the extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give a colourless solid (25.3 mg, 92 μmol, 37 % yield): mp 127-130 °C; IR ($CHCl_3$ cast) 3260, 2920, 1724, 1163 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40-7.9 (m, 5H, ArH), 6.95 (br. s, 1H, COOH), 5.75 (d, 1H, J=8.0 Hz, NH), 4.07 (dd, 1H, J=4.0, 8.0 Hz, CHN), 3.20 (m, 1H, $CHCH_3$), 1.68 (d, 1H, J=8.0 Hz, SH), 1.32 (d, 3H J=4.0 Hz, CH_3); FAB MS (glycerol/HCl) 276 (MH^+).

Methyl (*S*)-3-Methyl-2-[phenylsulfonyl(amino)]butanoate (7)

The literature procedure[120] for generation of analogous compounds was followed with the modifications outlined below. To a solution of **9** (4.85 g, 18.8 mmol) in Et_2O (25 mL) was added CH_2N_2 in Et_2O until the color turned light yellow. Acetic acid was added until the suspension was colourless. The solid was filtered, dissolved in $CHCl_3$ (10 mL) and washed with $NaHCO_3$ (5 %, 10 mL.) The organic layer was concentrated and dried *in vacuo* to give colourless crystals (63 g, 17.0 mmol, 90 % yield). A sample for combustion analysis was recrystallized from acetone/hexanes: mp 88.5-90 °C; IR ($CHCl_3$ cast) 3260, 2940, 1740, 1168 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.5-8.3 (m, 5H, ArH), 5.3 (d, 1H, J=10 Hz, NH), 3.9 (dd, 1H, J=6, 12 Hz, CHN), 3.55 (s, 3H, CO_2CH_3), 2.1 (m, 1H, J=8 Hz, $CH(CH_3)_2$), 1.0 (t, 6H, J=6 Hz, $(CH_3)_2$); MS (CI, NH_3) 289 (MNH_4^+); Anal. Calcd. for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.32; N, 5.16; Found: C, 52.90; H, 6.21; N, 5.27.

(*S*)-3-Methyl-2-[phenylsulfonyl(amino)]butanoic Acid (9)

The literature procedure[37] for generation of analogous compounds was modified: (*S*)-Valine **8** (5.26 g, 45.0 mmol), H_2O (60 mL), Na_2CO_3 (12.2 g, 115 mmol) and benzenesulfonyl chloride (8.5 mL, 67 mmol) were stirred at 20 °C for 5 h. The mixture was washed with Et_2O (50 mL) and the aqueous layer was acidified to pH 1 with HCl (6 M) and extracted with EtOAc (3 X 50 mL). The extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give the known **9** as a colourless powder (8.42 g, 32.8 mmol, 73 % yield): mp 136-138 °C (lit[37] mp 153 °C); IR (KBr disk) 3300, 2985, 1702, 1168 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.30-7.90 (m, 5H, ArH), 3.54 (d, 1H, J=5.4 Hz, CHN), 1.92 (m, 1H, J=6.6 Hz, $CH(CH_3)_2$), 0.84 (d, 3H, J=6.6 Hz, CH_3), 0.78 (d, 3H, J=6.6 Hz, CH_3); FAB MS (glycerol/HCl) 258 (MH^+).

(*S*)-Methyl 2-amino-3-methylbutanoate (10)[121]

A solution of **7** (2.71 g, 10.0 mmol) and Me_4NBr (4.62 g, 30.0 mmol) in CH_3OH (120 mL) was carefully poured onto Hg metal (25 g) equipped with an insulated Pt electrode (cathode). A porous frit containing H_2O (5 mL) and a carbon electrode (anode) was placed in the CH_3OH solution just above the surface of the mercury. Power (24 volts, 0.3 amps) was applied to the cell for 2.5 h. The methanolic solution was decanted, HCl (50 mL, 1M, 50 mmol) was added and the extract was washed with Et_2O (100 mL). The organic layer was concentrated *in vacuo* to give a colourless solid **7** (873 mg, 3.22 mmol, 32 % yield).

The aqueous layer plus extra H_2O (100 mL) was washed with Et_2O (2 X 100 mL), basified to pH 9 with NaOH (1M) and extracted with $CHCl_3$ (3 X 100 mL). The extracts were dried with Na_2SO_4 and concentrated *in vacuo* to give an oil **10** (419 mg, 3.20 mmol, 32 % yield): IR ($CHCl_3$ cast) 3380, 2985, 1740, 1164 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.74 (m, 1H, $C\underline{H}N$), 3.68 (s, 3H, $C\underline{H}_3$), 2.06 (m, 1H, $C\underline{H}(CH_3)_2$), 0.93 (d, 3H, J=7.0 Hz, $C\underline{H}_3$), 0.86 (d, 3H, J=7.0 Hz, $C\underline{H}_3$); FAB MS (glycerol/HCl) 132 (MH^+).

3-Phenyl-2-[phenylsulfonyl(amino)]propanoic Acid (11)

The literature procedure[37] for generation of analogous compounds was followed with the modifications outlined below: (*S*)-Phenylalanine (**12**) (1.71 g, 10.4 mmol), H_2O (100 mL), Na_2CO_3 (3.22 g, 30.4 mmol) and benzenesulfonyl chloride (2.0 mL, 2.8 g, 16 mmol) were stirred at 20 °C for 25 min. The mixture was filtered and the filtrate was washed with Et_2O (100 mL). The aqueous phase was acidified to pH 2 and washed with EtOAc (100 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo* to give the known **11** as colourless crystals (2.58 g, 8.46 mmol, 82 % yield): mp 131-132 °C; (lit[122] mp 133 °C); IR ($CHCl_3$ cast) 3330, 3050, 1730, 1169 cm^{-1}; ^{1}H NMR (200 MHz, CD_3COCD_3) δ 7.45-7.80 (m, 10H, $Ar\underline{H}$), 6.84 (br. d, 1H, J=7.0 Hz, $N\underline{H}$), 4.20 (br. dd, 1H, J=6.0, 7.0 Hz, $C\underline{H}$), 3.13 (dd, 1H, J=6.0, 12.5 Hz, $C\underline{H}HPh$); 3.00 (dd, 1H, J=7.0, 12.5 Hz, $CH\underline{H}Ph$); exact mass 305.0722 (305.0722 calcd. for $C_{15}H_{15}NO_4S$).

(*S*)-Phenylalanine (12)

The literature procedure[121] for generation of analogous compounds was modified: Compound **11** (1.53 g, 5.00 mmol), Me_4NCl (3.25 g, 29.7 mmol), and CH_3OH (35 mL) were placed over the mercury electrode and 21 volts (1 amp) was applied for 3 h. The methanolic solution was decanted, H_2O (50 mL) was added, and the mixture was filtered and concentrated *in vacuo*. Repeated (2 X) ion exchange chromatography (AG 50W-X8, 60 X 2.5 cm column, gradient elution H_2O - 1M NH_4OH) and lyophilization gave a

colourless powder (98.9 mg, 0.599 mmol, 12 % yield): mp 218-219 °C (lit[121] mp 270-275 °C); IR (KBr disk) 3430, 3030, 1600, 1405 cm^{-1}; ^{1}H NMR (200 MHz, D_2O) δ 7.30-7.60 (m, 5H, Ar$\underline{\mathrm{H}}$), 4.05 (dd, 1H, J=5.1, 7.9 Hz, C$\underline{\mathrm{H}}$N), 3.35 (dd, 1H, J=5.1, 14.4 Hz, C$\underline{\mathrm{H}}$H), 3.17 (dd, 1H, J=7.9, 14.4 Hz, CH$\underline{\mathrm{H}}$); FAB MS (glycerol/HCl) 166 (MH$^+$).

(*S*)-2-[4-Chlorophenylsulfonyl(amino)]-3-phenylpropanoic Acid (13)

The literature procedure[37] for generation of analogous compounds was modified: (*S*)-Phenylalanine (**12**) (1.69 g, 10.2 mmol), H_2O (100 mL), 4-chlorobenzenesulfonyl chloride (3.30 g, 15.6 mmol), and Na_2CO_3 (3.24 g, 30.6 mmol) were stirred at 20 °C for 40 min. The mixture was filtered and the precipitate was dissolved in CH_3OH, dried with Na_2SO_4 and concentrated *in vacuo*. Recrystallization from CH_3OH/H_2O gave colourless crystals (2.77 g, 8.15 mmol, 80 % yield): mp 91-94 °C; IR (KBr disk) 3440, 3080, 1740, 1157 cm^{-1}; ^{1}H NMR (360 MHz, CD_3OD) δ 7.64 (d, 2H, J=5.0 Hz, Ar$\underline{\mathrm{H}}$), 7.42 (d, 2H, J=5.0 Hz, Ar$\underline{\mathrm{H}}$), 7.12-7.22 (m, 5H, Ph$\underline{\mathrm{H}}$), 3.88 (dd, 1H, J=3.0, 4.7 Hz, C$\underline{\mathrm{H}}$), 3.05 (dd, 1H, J=3.0, 7.5 Hz, C$\underline{\mathrm{H}}$H), 2.84 (dd, 1H, J=4.7, 7.5 Hz, CH$\underline{\mathrm{H}}$); MS (CI, NH_3) 340 (MH$^+$).

(*S*)-2-[4-Nitrophenylsulfonyl(amino)]-3-phenylpropanoic Acid (14)

The literature procedure[123] for generation of analogous compounds was modified: (*S*)-Phenylalanine (**12**) (1.69 g, 10.2 mmol), H_2O (100 mL) 4-nitrobenzenesulfonyl chloride (3.19 g, 15.1 mmol), and Na_2CO_3 (3.15 g, 29.7 mmol) were stirred at 20 °C for 25 min. The mixture was filtered and the precipitate was washed with H_2O (20 mL). The precipitate was dissolved in CH_3OH and concentrated *in vacuo*. Recrystallization from CH_3OH/iPrOH gave crystals (1.70 g, 4.86 mmol, 48 % yield): mp 247-249 °C; IR (KBr disk) 3416, 3010, 1677, 1590 cm^{-1}; ^{1}H NMR (360 MHz, CD_3OD) δ 8.24 (d, 2H, J=5.0 Hz, Ar$\underline{\mathrm{H}}$), 7.88 (d, 2H, J=5.0 Hz, Ar$\underline{\mathrm{H}}$), 7.10-7.35 (m, 5H, Ph$\underline{\mathrm{H}}$), 3.92 (dd, 1H, J=4.8, 8.0 Hz, $C\underline{H}$), 3.10 (dd, 1H, J=4.8, 13.8 Hz, $C\underline{H}H$), 2.85 (dd, 1H, J=8.0, 13.8 Hz, $CH\underline{H}$); MS (CI, NH_3) 368 (MNH_4^+).

Methyl (*R*)-2-Amino-2-methyl-3-[phenylmethylthio]propanoate (16)

The literature procedure[22] for generation of analogous compounds was modified: Compound **25** (2.10 g, 6.29 mmol) in 0.50 M HCl (25 mL, 13 mmol) and CH_3CN (25 mL) was stirred for 12 days at 20 °C. Bulb to bulb distillation gave the known **16** as a colourless oil (1.05 g, 4.38 mmol, 70 % yield): bp 140 °C, 0.1 torr (lit[22] bp 100-110 °C, 0.1 torr); IR ($CHCl_3$ cast) 3460, 2970, 1735 cm^{-1}; ^1H NMR (360 MHz; $CDCl_3$) δ 7.30-7.35 (m, 5H, $Ar\underline{H}$), 3.74 (s, 2H, $C\underline{H}_2Ph$), 3.72 (s, 3H, $C\underline{H}_3$), 2.93 (d, 1H, J=13.3 Hz, $C\underline{H}HSBn$), 2.61 (d, 1H, J=13.2 Hz, $CH\underline{H}SBn$), 1.84 (s, 2H, $N\underline{H}_2$), 1.35 (s, 3H, $CC\underline{H}_3$); exact mass 239.0983 (239.0980 calcd. for $C_{12}H_{17}NO_2S$).

(2*S*,5*S*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-5-methylpyrazine (18)

Trimethyloxonium tetrafluoroborate (37.0 g, 250. mmol) was added to **23** (16.3 g, 95.9 mmol) in dichloromethane (500 mL) and the mixture was stirred for 2 days. Compound **24** (14.2 g, 96.1 mmol) was added and the mixture was stirred for 1 day. A solution of $NaH_2PO_4{\cdot}H_2O$ (49.7 g, 360. mmol) and $Na_2HPO_4{\cdot}H_2O$ (169 g, 1.05 mol) in 1 L water was added and the layers were separated. The aqueous phase was washed with CH_2Cl_2 (3 X 600 mL) and the pooled organic phases were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Distillation gave the known **18** as a clear colourless liquid (12.6 g, 63.5 mmol, 66 % yield): bp 80-115 °C, 10 torr (lit[43] bp 83-85 °C, 8-10 torr); IR ($CHCl_3$ cast) 2960, 1696, 1239 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.08 (m, 1H, $C\underline{H}CH_3$), 3.98 (t, 1H, J=2.0 Hz, $C\underline{H}(CH_3)_2$), 3.66 (s, 3H, $C\underline{H}_3$), 3.68 (s, 3H, $C\underline{H}_3$), 2.20 (m, 1H, $C\underline{H}CH_3$), 1.38 (d, 3H, J=3.0 Hz, $C\underline{H}_3CH$), 1.03 (dd, 3H, J=2.0, 4.0 Hz, $C\underline{H}_3$), 0.72 (t, 3H, J=4.0 Hz, $C\underline{H}_3$); exact mass 198.1368 (198.1368 calcd. for $C_{10}H_{18}N_2O_2$); Anal calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found C, 60.51; H, 9.18; N, 13.97.

Methyl (*S*)-2-Aminopropanoate Hydrochloride (20)

The literature procedure[124] for the generation of analogous compounds was followed. To a suspension of (*S*)-alanine (**21**) (36.0 g, 0.404 mol) and CH_3OH (700 mL, 17.3 mol) at 0 °C was added HCl gas until the colourless solid dissolved (30 min). The solution was kept at 0 °C for 24 h, the methanolic portion of the solvent was removed *in vacuo*, dry Et_2O (250 mL) was added, and the mixture was stored at 0 °C for 24 h. The solid was filtered, washed with Et_2O (250 mL) and dried over P_4O_{10} to give the known **20** as colourless crystals (41.8 g, 0.299 mol, 74 % yield): mp 106-109 °C (lit mp 154-155 °C[122], 109-110 °C[122]; authentic standard from Sigma mp 110-111 °C); IR ($CHCl_3/CH_3OH$ cast) 2960, 2000, 1746, 1250 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 4.12 (m, 1H, J=8.0 Hz, $C\underline{H}$), 3.84 (s, 3H, $C\underline{H}_3$), 1.55 (d, 3H, J=8.0 Hz, $C\underline{H}_3CH$); exact mass 103.0637 (103.0633 calcd. for $C_4H_9NO_2$); Anal. Calcd for $C_4H_{10}NO_2Cl$: C, 34.42; H, 7.22; N, 10.03. Found: C, 34.66; H, 7.29; N, 9.88.

(3*S*,6*S*)-3-Isopropyl-6-methylpiperazine-2,5-dione (23)

The literature procedure[43] was followed. (*S*)-Valine (**8**) (46.8 g, 0.400 mol) in THF (600 mL) and phosgene (29.5 mL, 42.2 g, 0.431 mol) gave 106 g (0.738 mol, 185 % mass balance) of a green syrup. (*S*)-Valine *N*-carboxyanhydride (**19**) was used below without further purification.

Triethylamine (125 mL, 90.8 g, 0.900 mol) was added to **20** (55.8 g, 0.400 mol) in $CHCl_3$ (490 mL). The *N*-carboxyanhydride **19** (57.2 g, 0.400 mol) in dry THF (400 mL) was then added. The (*S*)-valinyl-(*S*)-alanine methyl ester (**22**) was used below without further purification.

A solution of **22** was dissolved in $PhCH_3$ (1.7 L) and heated to reflux for 12 h. The mixture was then stored at 0 °C for 4 h. The precipitate was filtered, washed with cold Et_2O, and dried at 90 °C for 2 days to give the known **23** as a powder (32.5 g, 0.191 mol, 48 % yield over 2 steps) which was used directly in the preparation of **18**: mp 245-246 °C (dec.) (lit[43] mp 254 °C); IR (KBr disk) 3200, 2970, 2600, 2500, 1672 cm^{-1}; ^1H NMR (200 MHz, CD_3SOCD_3) δ 8.12 (s, 1H, N$\underline{H}$), 7.99 (s, 1H, N$\underline{H}$), 3.87 (q, 1H, J=7.0, 7.3 Hz, C$\underline{H}$CH$_3$), 3.67 (m, 1H, C$\underline{H}$NCH), 2.14 (m, 1H, C$\underline{H}$CHN), 1.26 (d, 3H, J=7.0 Hz, C$\underline{H}_3$CH), 0.92 (d, 3H, J=7.0 Hz, C$\underline{H}_3$), 0.82 (d, 3H, J= 7.0 Hz, C$\underline{H}_3$); exact mass 156.0898 (156.0899 calcd. for $C_8H_{14}N_2O_2$).

Trimethyloxonium Fluoroborate (24)

The literature procedure[44] was followed. Dimethyl ether (150 mL, 243 g, 5.29 mol) was condensed into a solution of freshly distilled boron trifluoride etherate (68 mL, 78 g, 0.56 mol) in dichloromethane (160 mL). Epichlorohydrin (48 mL, 57 g, 0.61 mol) was added dropwise over 15 min. The mixture was stirred for 3 h, and the solvent was removed *in vacuo*. The colourless solid was washed with CH_2Cl_2 (2 X 200 mL) and then Et_2O (2 X 200 mL) to give colourless crystals (54.3 g, 0.368 mol, 88 % yield): mp 197-201 °C (lit mp 179.5-180,[44] 124.5,[125] 141-143,[126] 175 °C[127]).

(2S,5S)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-methyl-5-phenylmethylthiomethylpyrazine (25)

The literature procedure[22] for the generation of analogous compounds was followed. Benzylthiol (27) (2.7 mL, 2.9 g, 23 mmol) was added to potassium *tert*-butoxide (2.46 g, 22.0 mmol) in DMSO (67 mL) followed by **28** (5.01 g, 20.0 mmol) in DMSO (13 mL), and the mixture was warmed to 70 °C for 6 h. Hexanes (200 mL) were added and the mixture was washed with H_2O (60 mL). The aqueous phase was washed with hexanes (3

X 200 mL) and the pooled organic phases were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash cromatography (hexanes:EtOAc 19:1) gave an oil (5.30 g, 19.9 mmol, 79 % yield): IR ($CHCl_3$ cast) 3000, 1695, 1240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5H, $Ar\underline{H}$), 4.09 (d, 1H, J=3.3 Hz, $C\underline{H}N$), 3.69 (s, 3H, $C\underline{H}_3$), 3.67 (s, 3H, $C\underline{H}_3$), 3.66 (s, 2H, $SC\underline{H}_2Ph$), 2.91 (d, 1H, J=13.4 Hz, $CC\underline{H}H$), 2.67 (d, 1H, J=13.4 Hz, $CC\underline{H}H$), 2.29 (m, 1H, $C\underline{H}(CH_3)_2$), 1.36 (s, 3H, $C\underline{H}_3C$), 1.10 (d, 3H, J=6.8 Hz, $C\underline{H}_3CH$), 0.69 (d, 3H, J=6.8 Hz, $C\underline{H}_3CH$); exact mass 334.1715 (334.1715 calcd. for $C_{18}H_{26}N_2O_2S$).

Bromomethyl Benzyl Sulfie (26)

The literature procedure[45, 46] was followed: To a suspension of paraformaldehyde (7.57 g, 0.252 mol) in benzene (50 mL) at 24 °C was added 48 % HBr (142 mL, 215 g, 1.28 mol) over 5 min. After 20 min, the temperature was changed to 38 °C and benzylthiol (27) (23.5 mL, 24.9 g, 0.201 mol) was added. The solution was stirred at 50 °C for 3 h. The benzene layer was separated, washed with H_2O (50 mL) and brine (50 mL), and dried over Na_2SO_4. The solution was filtered, concentrated, and distilled under reduced pressure to give the known 26 as a colourless liquid (27.5 g, 127 mmol, 63 % yield): bp 75 °C, 0.35 torr (lit[45] bp 75-81 °C, 0.1 torr); IR ($CHCl_3$ cast) 3020, 1490, 1450, 1181, 734, 699 cm^{-1}; ^1H NMR (200 MHz, CD_2Cl_2) δ 7.45-7.25 (m, 5H, $Ar\underline{H}$), 4.52 (s, 2H, $C\underline{H}_2Br$), 3.94 (s, 2H, $C\underline{H}_2Ph$); exact mass 137.042 (137.0425 calcd. for C_8H_9S).

(2*S*,5*S*)-5-Bromomethyl-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-methylpyrazine (28)

The literature procedure[22] for the generation of analogous compounds was followed. BuLi (8.4 mL, 13 mmol) was added to **18** (2.27 g, 11.5 mmol) in THF (25 mL) at -78 °C over 5 min. After 15 min dibromomethane (26.2 g, 151. mmol) in THF (15 mL) was added. The crude organic phase was bulb to bulb distilled to give an oil (3.03 g, 10.4 mmol, 91 % yield): bp 80 °C, 0.4 torr (lit[22] bp 70-80 °C, 0.1 torr); IR ($CHCl_3$ cast) 2960, 1697, 1215 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.03 (d, 1H, J=3.0 Hz, $C\underline{H}N$), 3.76 (d, 1H, J=9.5 Hz, $C\underline{H}HBr$), 3.70 (s, 3H, $C\underline{H}_3$), 3.69 (s, 3H, $C\underline{H}_3$), 3.40 (d, 1H, J=9.5 Hz, $CH\underline{H}Br$), 2.29 (d sept, 1H, J=4.0, 8.0 Hz, $C\underline{H}(CH_3)_2$), 1.45 (s, 3H, $CC\underline{H}_3$), 1.09 (d, 3H, J=7.0 Hz, $CHC\underline{H}_3$), 0.68 (d, 3H, J=7.0 Hz, $CHC\underline{H}_3$); exact mass 292.0607 (290.0630 calcd. for $C_{11}H_{19}N_2O_2Br$); Anal Calcd. for $C_{11}H_{19}N_2O_2Br$: C, 45.37; H, 6.58; N, 9.62. Found: C, 45.43; H, 6.56; N, 9.51.

(2*R*,5*S*)- and (2*S*,5*S*)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-methyl-5-phenylmethylthiomethylpyrazine (29)

The literature procedure[22] for the generation of analogous compounds was followed. Benzylthiol (**27**) (1.70 mL, 1.80 g, 14.5 mmol), potassium *tert*-butoxide (1.53 g, 13.7 mmol) in DMSO (29.5 mL) and **28** (3.61 g, 12.4 mmol) in DMSO (8 mL) were warmed to 75 °C for 6.5 h. Hexanes (110 mL) were added and the mixture was washed with H_2O (40 mL). The aqueous phase was washed with hexanes (3 X 80 mL), and the pooled organic phases were dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 19:1) gave an oil (2.50 g, 7.48 mmol, 60 % yield) as a mixture of diastereomers: IR ($CHCl_3$ cast) 2970, 1694, 1216, 759 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20-7.35 (m, 5H, $Ar\underline{H}$), 4.09 & 3.91 (2 X d, 1H, 2 X J=3.4 Hz, $C\underline{H}N$), 3.71, 3.68, 3.67 & 3.66 (4 X s, 8H, 2 X $C\underline{H}_3$ & 2 X $SC\underline{H}_2Ph$), 2.91 (d, 1H, J=13.3 Hz, $CC\underline{H}H$), 2.71 & 2.67 (2 X d, 1H, 2 X J=13.4 Hz, $CCH\underline{H}$), 2.30 (m, 1H,

$C\underline{H}(CH_3)_2$), 1.36 & 1.30 (2 X s, 3H, $CC\underline{H}_3$), 1.13 & 1.10 (2 X d, 3H, J=6.1, 6.8 Hz, $C\underline{H}_3CH$), 0.80 & 0.69 (2 X d, 3H, 2 X J=6.7 Hz, $C\underline{H}_3CH$); exact mass 334.1715 (334.1715 calcd. for $C_{18}H_{26}N_2O_2S$).

Methyl (*R*)-2-Amino-2-methyl-3-phenylmethylthiopropanoate (31)

The literature procedure[22] was followed using the amounts outlined below. Compound 37 (110. mg, 0.328 mmol) was dissolved in 0.25 M HCl (2.6 mL, 0.66 mmol) and stirred for 12 days at 20 °C. Ether (10 mL) was added, the layers were separated and the aqueous layer was lyophilized. The residue was dissolved in H_2O (5 mL) and Et_2O (3 mL) was added. Concentrated aqueous ammonium hydroxide was added to bring to pH to 8.3, the layers were separated, and the aqueous phase was extracted with Et_2O (3 X 3 mL). The pooled organic phases were dried with $MgSO_4$, filtered, concentrated *in vacuo* and bulb to bulb distilled to give 8.63 g (36.1 μmol, 11 % yield): bp 85-105 °C, 1 torr (lit[22] bp 100-110 °C, 0.1 torr); $[\alpha]_D$=-37° (*c*=0.56, 95 % ethanol) (lit[22] $[\alpha]_D$=-33° (*c*=1.1, ethanol)); IR ($CHCl_3$ cast) 3390, 2980, 1735, 1200 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5H, $Ar\underline{H}$), 3.74 (s, 2H, $C\underline{H}_2Ph$), 3.72 (s, 3H, $C\underline{H}_3$), 2.93 (d, 1H, J=13.3 Hz, $CC\underline{H}H$), 2.61 (d, 1H, J=13.2 Hz, $CCH\underline{H}$), 1.35 (s, 3H, $CC\underline{H}_3$); exact mass 239.0980 (239.0980 calcd. for $C_{12}H_{17}NO_2S$); Anal. Calcd. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 59.62; H, 7.17; N, 5.79.

(3*R*,6*S*)-3-Isopropyl-6-methylpiperazine-2,5-dione (34)

The literature procedure[43] was modified. To a solution of (*R*)-valine (30) (46.9 g, 0.401 mol) in THF (600 mL) was bubbled phosgene (30 mL, 43 g, 0.44 mol) at 40 °C over 3 h. Ar was then bubbled through, the solution was filtered and concentrated *in vacuo* to give 76.5 g (0.534 mol, 133 % mass balance) of a green syrup. The (*R*)-Valine *N*-carboxyanhydride (32) was used below without further purification.

The literature procedure[43] was modified. To a stirred solution of **28** (56.0 g, 0.402 mol) in $CHCl_3$ (500 mL) at -68 °C was added triethylamine (125 mL, 90.8 g, 0.900 mol). Compound **32** (76.5 g, 0.401 mol) in dry THF (400 mL) was added via canula and the solution was warmed to 20 °C. The mixture was filtered through a sintered glass funnel, concentrated *in vacuo*, then diluted twice with $PhCH_3$ (200 mL) and concentrated *in vacuo*. The dipeptide ester (*R*)-Val-(*S*)-Ala-OCH_3 (**33**) was used in the preparation of **34** without further purification.

A solution of **33** dissolved in $PhCH_3$ (1.7 L) was heated to reflux with mechanical stirring for 10.5 h and then kept at 0 °C for 4 h. The precipitate was filtered, washed with cold Et_2O, and dried in a vacuum oven for 24 h to give the known **34** as a powder (41.1 g, 0.241 mol, 61 % yield over 2 steps) which was used directly in the preparation of **35**: mp 243-248 °C (dec.) (lit[43] mp 254 °C); IR (KBr disk) 3190, 2960, 1670 cm^{-1}; ^1H NMR (200 MHz, CD_3SOCD_3) δ 8.11 (s, 2H, 2 X NH), 3.90 (q, 1H, J=6.0 Hz, $CHCH_3$), 3.51 (t, 1H, J=4.0 Hz, CHNCH), 2.10 (m, 1H, CHCHN), 1.21 (d, 3H, J=6.0 Hz, CH_3CH), 0.87 (dd, 6H, J=6.0, 14.0 Hz, $(CH_3)_2$); exact mass 170.1050 (170.1055 calcd. for $C_8H_{14}N_2O_2$).

(2*R*,5*S*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-5-methylpyrazine (35)

The literature procedure[43] was modified. To a solution of **34** (21.0 g, 123 mmol) in dichloromethane (500 mL) was added **24** (46.0 g, 311 mmol) and the mixture was stirred at 20 °C for 2 days. Compound **24** (19.2 g, 130 mmol) was added and the mixture was stirred at 20 °C for 1 day. A solution of $NaH_2PO_4 \cdot H_2O$ (69.7 g, 500 mmol) and $Na_2HPO_4 \cdot H_2O$ (168 g, 1.05 mol) in H_2O (1 L) was added, the aqueous layer was washed 3 times with CH_2Cl_2 (600 mL). The organic layers were pooled, and dried with $MgSO_4$. This solution was filtered, concentrated *in vacuo*, and distilled to give the known **35** as a colourless liquid (12.6 g, 63.5 mmol, 52 % yield): bp 80 °C, 10 torr (lit[43] bp 83-85 °C, 8

10 torr); IR ($CHCl_3$ cast) 2971, 1695, 1240, 759 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.04 (m, 1H, C$\underline{H}$CH$_3$), 3.98 (t, 1H, J=4.0 Hz, C$\underline{H}$NCH), 3.71 (s, 3H, C$\underline{H}_3$), 3.68 (s, 3H, C$\underline{H}_3$), 2.25 (m, 1H, C$\underline{H}$CHN), 1.37 (d, 3H, J=7.0 Hz, C$\underline{H}_3$CH), 1.05 (d, 3H, J=7.0 Hz, C$\underline{H}_3$), 0.70 (d, 3H, J=7.0 Hz, C$\underline{H}_3$); exact mass 198.1368 (198.1368 calcd. for $C_{10}H_{18}N_2O_2$; Anal calcd. for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found C, 61.08; H, 9.17; N, 14.09.

(2*R*,5*R*)-5-Bromomethyl-2,5-dihydro-2-isopropyl-3,6-dimethoxy-5-methylpyrazine (36)

The literature procedure[22] was followed using the amounts outlined below: To **35** (5.51 g, 27.8 mmol) in THF (45 mL) at -78 °C was added BuLi (20 mL, 30 mmol) over 5 min. After 15 min dibromomethane (52.3 g, 301 mmol) was added dropwise over 7 min. After 48 h, the solvent was removed *in vacuo*, the residue was taken up in Et_2O (120 mL) and washed with H_2O (90 mL). The aqueous phase was extracted with Et_2O (3 X 60 mL), and the pooled organic phases were dried with $MgSO_4$, filtered, concentrated *in vacuo*, and bulb to bulb distilled: bp 85 °C, 0.5 torr. Flash chromatography (hexanes:EtOAc 19:1) gave the known **36** as an oil (3.96 g, 13.6 mmol, 49 % yield): IR (neat film) 3000, 1696, 1215, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.03 (d, 1H, J=3.4 Hz, C$\underline{H}$N), 3.76 (d, 1H, J=9.4 Hz, C$\underline{H}$HBr), 3.71 (s, 3H, C$\underline{H}_3$), 3.69 (s, 3H, C$\underline{H}_3$), 3.40 (d, 1H, J=9.4 Hz, CH$\underline{H}$Br), 2.29 (m, 1H, J=4.0 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.45 (s, 3H, CC$\underline{H}_3$), 1.09 (d, 3H, J=6.9 Hz, CHC$\underline{H}_3$), 0.68 (d, 3H, J=6.9 Hz, CHC$\underline{H}_3$); exact mass 290.0619 (290.0630 calcd. for $C_{11}H_{19}N_2O_2Br$); Anal Calcd. for $C_{11}H_{19}N_2O_2Br$: C, 45.37; H, 6.58; N, 9.62. Found: C, 45.43; H, 6.56; N, 9.51.

(2*R*,5*R*)-2,5-Dihydro-2-isopropyl-3,6-dimethoxy-5-methyl-5-phenylmethylthiomethylpyrazine (37)

The literature procedure[22] was followed using the amounts outlined below: Benzylthiol (**27**) (1.8 mL, 1.9 g, 15 mmol) was added to a stirred suspension of potassium *tert*-butoxide (1.60 g, 14.3 mmol) in DMSO (43 mL). After 15 min a solution of **36** (3.58 g, 12.3 mmol) in DMSO (9 mL) was added, and the mixture was warmed to 70 °C for 7 h. Hexanes (120 mL) were added and the mixture was washed with H_2O (40 mL). The aqueous phase was washed with hexanes (3 X 80 mL), and the organic phases were pooled, dried with $MgSO_4$, filtered and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 19:1) gave the known **37** as an oil (3.21 g, 9.60 mmol, 78 % yield). IR ($CHCl_3$ cast) 2980, 1694, 1234 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20-7.35 (m, 5H, Ar$\underline{H}$), 4.09 (d, 1H, J=3.4 Hz, C$\underline{H}$N), 3.68 (s, 3H, C$\underline{H}_3$), 3.67 (s, 3H, C$\underline{H}_3$), 3.66 (s, 2H, SC$\underline{H}_2$Ph), 2.91 (d, 1H, J=13.3 Hz, CC$\underline{H}$H), 2.67 (d, 1H, J=13.4 Hz, CCH$\underline{H}$), 2.31 (m, 1H, C$\underline{H}(CH_3)_2$), 1.36 (s, 3H, C$\underline{H}_3$C), 1.10 (d, 3H, J=6.8 Hz, C$\underline{H}_3$CH), 0.69 (d, 3H, J=6.8 Hz, C$\underline{H}_3$CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.80 ($\underline{C}$=N), 163.01 ($\underline{C}$=N), 138.72 (Ar$\underline{C}$), 128.85 (Ar$\underline{C}$), 128.33 (Ar$\underline{C}$), 126.78 (Ar$\underline{C}$), 61.35 (O$\underline{C}H_3$), 59.82 (O$\underline{C}H_3$), 52.25 (C$\underline{C}$HN), 52.15 ($\underline{C}$HNCH), 42.99 ($\underline{C}$HCHN), 37.10 (C$\underline{C}H_3$), 30.87 ($\underline{C}H_3$), 27.90 ($\underline{C}H_3$), 19.35 (C$\underline{H}_2$Ph), 16.84 (C$\underline{C}H_2$S); exact mass 334.1716 (334.1715 calcd. for $C_{18}H_{26}N_2O_2S$).

(2*RS*,5*R*)-2,5-Dihydro-3,6-dimethoxy-2-isopropyl-5-methyl-5-phenylmethylthiomethylpyrazine (38)

The literature procedure[22] for the generation of analogous compounds was followed. Benzylthiol (**27**) (2.50 mL, 2.70 g, 21.4 mmol), potassium *tert*-butoxide (2.28 g, 20.2 mmol) in DMSO (60 mL) and **36** (5.35 g, 18.4 mmol) in DMSO (12 mL) were warmed to 70 °C for 4.5 h and stirred overnight at 20 °C. Flash chromatography (hexanes:EtOAc 19:1) gave an oil (4.27 g, 12.8 mmol, 70 % yield) as a mixture of diastereomers. IR ($CHCl_3$ cast) 2980, 1696, 1241 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.18-7.35 (m, 5H, Ar$\underline{H}$), 4.09 & 3.91 (2 X d, 1H, 2 X J=3.2 Hz, C$\underline{H}$N), 3.62-3.74 (4 X s, 8H, 2 X CH_3 & 2 X SC$\underline{H}_2$Ph), 2.90 (d, 1H, J=13.4 Hz, CC$\underline{H}$H), 2.72 & 2.67 (2 X d, 1H, 2 X J=13.4 Hz, CCH$\underline{H}$), 2.36 & 2.29 (2 X m, 1H, C$\underline{H}(CH_3)_2$), 1.36 & 1.31 (2 X s, 3H, CC$\underline{H}_3$), 1.13 & 1.10 (2 X d, 3H, J=6.8, 7.1 Hz, C$\underline{H}_3$CH), 0.80 & 0.69 (2 X d, 3H, 2 X J=6.8 Hz, C$\underline{H}_3$CH); exact mass 334.1716 (334.1715 calcd. for $C_{18}H_{26}N_2O_2S$).

(*R*)-2-Amino-2-methyl-3-phenylmethylthiopropanoic Acid (40) By Dilute Acid Hydrolysis of 37.

A solution of **37** (2.75 g, 8.23 mmol) was dissolved in HCl (0.25 M, 66 mL, 17 mmol) and CH_3CN (5.7 mL), and was then stirred for 15 days at 20 °C. The solution was extracted with Et_2O (30 mL), and the aqueous phase was lyophilized to give a colourless powder. This was stirred in a solution of $LiOH{\cdot}H_2O$ (16.9 g, 400. mmol) in H_2O (200 mL) for 16 days at 20 °C. After lyophilization the sample was eluted from an AG 50 ion exchange column with 1M NH_4OH. Separation by MPLC (RP8, Merck Lobar, flow=2.3 mL/min, 40 % CH_3OH/H_2O, t_R=140 min), and AG 50 ion exchange eluted with 1 M HCl gave colourless crystals (38.1 mg, 0.169 mmol, 2 % yield): mp 154-160 °C; IR (KBr disk) 3420, 3000, 1622, 1584 cm^{-1}; ^1H NMR (360 MHz, D_2O) δ 7.30-7.45 (m, 5H, Ar$\underline{H}$), 3.82 (s, 2H, PhC$\underline{H}_2$), 3.04 (d, 1H, J=14.0 Hz, C$\underline{H}$HSBn), 2.62 (d, 1H, J=14.0

Hz, CH$\underline{H}$SBn), 1.32 (s, 3H, C$\underline{H}_3$); FAB MS (Cleland) 226 (MH^+-Cl); Anal. Calcd for $C_{11}H_{16}NO_2SCl$: C, 50.47; H, 6.16; N, 5.35. Found: C, 50.50; H, 5.34; N, 5.00.

(*R*)-2-Amino-2-methyl-3-phenylmethylthiopropanoic Acid (40) By Concentrated Acid Hydrolysis of 37.

A solution of **37** (87 mg, 0.26 mmol) was heated to reflux in HCl (6M, 5 mL, 30 mmol) for 7 h. It was diluted with 20 mL H_2O and extracted with Et_2O (10 mL). The aqueous phase was lyophilized to near dryness. Colourless crystals separated and were purified on a cation exchange AG 50 column with 1M NH_4OH. After lyophilization to near dryness, colourless crystals separated (20. mg, 90. μmol, 34 % yield): IR (KBr disk) 3440, 3020, 1735, 1492 cm^{-1}; ^1H NMR (200 MHz, DCl/D_2O) δ 7.30-7.50 (m, 5H, Ar$\underline{H}$), 3.87 (s, 2H, PhC$\underline{H}_2$S), 3.20 (d, 1H, J=16.0 Hz, C$\underline{H}$HSBn), 3.05 (d, 1H, J=15.0 Hz, CH$\underline{H}$SBn), 1.66 (s, 3H, C$\underline{H}_3$); FAB MS 226 (MH^+-Cl).

(*R*)-2-Amino-2-methyl-3-phenylmethylthiopropanoic Acid (40) From 31.

The literature procedure[52] for the generation of analogous compounds was followed. A solution of **31** (232 mg, 971 μmol) in acetone (3.5 mL) and HCl (3.4 mL, 3.9 M, 13 mmol) was heated to reflux for 75 min. The mixture was concentrated *in vacuo*, and saturated $NaHCO_3$ was added until bubbling ceased. The mixture was filtered and extracted with $CHCl_3$ (10 mL). The aqueous layer was concentrated *in vacuo* and conc. HCl was added until the pH was ≤ 2.5. Separation by AG 50 ion exchange (eluted with 1 M NH_4OH) and lyophilization gave colourless crystals (28.5 mg, 0.127 mmol, 13 % yield, 35 % based on recovered starting material): mp 200, 224-231 °C (dec.); IR (KBr disk) 3440, 3000, 1624 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 7.35-7.45 (m, 5H, Ar$\underline{H}$), 3.85 (s, 2H, PhC$\underline{H}_2$), 3.16 (d, 1H, J=13.0 Hz, C$\underline{H}$HSBn), 2.93 (d, 1H, J=13.0 Hz, CH$\underline{H}$SBn), 1.59 (s, 3H, C$\underline{H}_3$); FAB MS (glycerol/HCO_2H) 226 (MH^+-Cl).

(*R*)-2-Amino-2-methyl-3-phenylmethylthiopropanoic Acid (40) By Basic Hydrolysis of 31.

The literature procedure[128] for the generation of analogous compounds was followed. A solution of **31** (32.5 mg, 0.136 mmol) in CH_3OH (0.27 mL) and NaOH (1M, 0.15 mL, 0.15 mmol) was stirred at 20 °C, for 90 min. The solution was concentrated *in vacuo*, 1M HCl was added to bring the pH to ≤ 2.5 and the mixture was stored at 0 °C. The precipitate was filtered, recrystallized from boiling ethanol, and centrifuged to give colourless crystals (3.7 mg, 14 μmol, 11 % yield): IR (KBr disk) 3440, 2980, 1756, 1505 cm^{-1}; ^1H NMR (200 MHz, DCl) δ 7.35-7.45 (m, 5H, Ar$\underline{H}$), 3.85 (s, 2H, PhC$\underline{H}_2$), 3.16 (d, 1H, J=13.0 Hz, C$\underline{H}$HSBn), 2.93 (d, 1H, J=13.0 Hz, CH$\underline{H}$SBn), 1.59 (s, 3H, C$\underline{H}_3$); FAB MS (Cleland) 226 (MH^+-Cl).

(*R*)-2-Amino-2-methyl-3-phenylmethylthiopropanoic Acid (40) By Iodotrimethylsilane Deprotection.

The literature procedure[129, 130] for the generation of analogous compounds was followed. To a solution of **31** (38.8 mg, 0.162 mmol) in tetrahydrothiophene-1,1-dioxide (0.5 mL), was added iodotrimethylsilane (0.06 mL, 80 mg, 0.4 mmol), and the solution was heated to 80 °C for 1h. $CHCl_3$ (1 mL) was added and the mixture was extracted with H_2O (2 mL). The organic layer was extracted with H_2O (3 X 1 mL) and the aqueous phase was concentrated *in vacuo*. The residue from the aqueous phase was partitioned between Et_2O (10 mL) and H_2O (3 X 1 mL). The combined aqueous phases were separated on an ion exchange (AG 50) column with 1 M NH_4OH to give colourless crystals (7.3 mg, 32 μmol, 20 % yield). Spectral properties were identical to those of **31** obtained above by acidic hydrolysis.

(*S*)-2-Amino-2-methyl-3-phenylmethylthiopropanoic Acid Hydrochloride Salt (41)

The literature procedure[52] for the generation of analogous compounds was followed. A solution of **16** (478 mg, 2.00 mmol) in acetone (7 mL) and HCl (6.8 mL, 5.7 M) was heated to reflux for 42 h. Concentration *in vacuo*, dilution with H_2O, and concentration *in vacuo* gave crystals (557 mg, 2.47 mmol, 124 % mass balance): IR (KBr disk) 3440, 2980, 1624, 1495 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 7.35-7.45 (m, 5H, Ar$\underline{H}$), 3.85 (s, 2H, PhC$\underline{H}_2$), 3.16 (d, 1H, J=13.0 Hz, C$\underline{H}$HSBn), 2.93 (d, 1H, J=13.0 Hz, CH$\underline{H}$SBn), 1.59 (s, 3H, C$\underline{H}_3$); FAB MS (Cleland) 226 (MH^+-Cl).

(*R*)-*S*-Phenylmethylcysteinylglycine *tert*-Butyl Ester Trifluoroacetate Salt (45)

The literature procedure[48] for generation of analogous compounds was modified. Compound **43** (3.10 g, 14.7 mmol) was stirred with dioxane (75 mL) at 44 °C and phosgene (3 mL, 4 g, 40 mmol). After 30 min, a stream of Ar was bubbled through the solution overnight. The Leuch's anhydride solution was filtered and concentrated *in vacuo*. The residue was dissolved in THF (15 mL) and cooled to -78 °C. To a solution of glycine *t*-butyl ester hydrochloride **44** (2.46 g, 14.7 mmol) and $CHCl_3$ (20 mL) at -60 °C was added *N*-methylpiperidine (2.8 mL, 2.3 g, 23 mmol). The cysteine Leuch's anhydride was added via canula to the glycine ester, and the mixture was stirred at -60 °C for 5 h, during which time a colourless precipitate formed. TFA (3 mL) was added and the solution was allowed to warm overnight to 20 °C. The mixture was concentrated *in vacuo* and separated on an MPLC column (RP8, Merck Lobar, 30 % CH_3OH/H_2O (0.1 % TFA), flow=3 mL/min) to give a colourless oil (33.8 mg, 740 μmol, 20 % yield): IR ($CHCl_3$ cast) 2982, 1740, 1673, 1203 cm^{-1}; ^1H NMR (200 MHz, CD_3CN) δ 7.74 (br d, 1H, N$\underline{H}$), 7.20-7.40 (m, 5H, Ar$\underline{H}$), 4.21 (t, 1H, J=6.0 Hz, C$\underline{H}$CH$_2$), 3.90 (dd, 1H, J=4.0, 6.0 Hz, C$\underline{H}$HN), 3.80 (s, 2H, C$\underline{H}_2$Ph), 3.79 (dd, 1H, J=4.0, 6.0 Hz, CH$_2$N$\underline{H}$), 3.02

(dd, 1H, J=6.0, 15.5 Hz, C$\underline{H}$HCH), 2.89 (dd, 1H, J=6.0, 15.5 Hz, CH$\underline{H}$CH), 1.44 (s, 9H, $(C\underline{H}_3)_3$); exact mass 324.1506 (324.1508 calcd. for $C_{16}H_{24}N_2O_3S$); Anal. Calcd. for $C_{18}H_{27}F_3N_2O_6S$: C, 47.36; H, 5.96; N, 6.14. Found: C, 47.96; H, 5.68; N, 6.14.

(*R*)-*S*-Phenylmethyl-α-methylcysteinylglycine *tert*-Butyl Ester Trifluoroacetate Salt (47)

The literature procedure[48] for generation of analogous compounds was modified. Crude **40** (503 mg, 1.05 mmol) was dissolved in dioxane (5 mL) and phosgene (4.0 mL, 5.7 mg, 58 mmol) was distilled into the flask. The mixture was stirred at 20 °C for 4 days, THF (2 mL) was added, and the solution was cooled to -78 °C. A solution of glycine *t*-butyl ester hydrochloride (**44**) (207 mg, 1.24 mmol) and *N*-methylpiperidine (0.13 mL, 106 mg, 1.07 mmol) in $CHCl_3$ (2 mL) and THF (0.5 mL) at -78 °C was added, and the solution was allowed to warm to 20 °C overnight. The mixture was heated to 50 °C for 1 h and *p*-toluenesulfonic acid (0.46 g) in ethanol (3 mL) was added. The mixture was separated on an MPLC column (RP8, Merck Lobar, 50 % CH_3OH/H_2O(0.1 % trifluoroacetic acid)) to give an oil (299 mg, 662 μmol, 63 % yield): IR (CH_2Cl_2 cast) 2983, 1742, 1671, 1203 cm^{-1}; ^1H NMR (360 MHz, CD_3OD) δ 7.16-7.36 (m, 5H, Ar$\underline{H}$), 3.92 (d, 1H, J=17.4 Hz, NC$\underline{H}$H), 3.84 (s, 2H, $C\underline{H}_2Ph$), 3.81 (d, 1H, J=17.5 Hz, NCH$\underline{H}$), 3.11 (d, 1H, J=14.4 Hz, C$\underline{H}$HSBn), 3.00 (d, 1H, J=14.4 Hz, CH$\underline{H}$SBn), 1.64 (s, 3H, $NCC\underline{H}_3$), 1.45 (s, 9H, $C(C\underline{H}_3)_3$); exact mass 338.1673 (338.1664 calcd. for $C_{17}H_{26}N_2O_3S$); Anal. Calcd. for $C_{19}H_{27}F_3N_2O_5S$: C, 50.43; H, 6.01; N, 6.19. Found: C, 50.03; H, 5.92; N, 5.98.

(*S*)-*S*-Phenylmethyl-α-methylcysteinylglycine *t*-Butyl Ester Trifluoroacetate Salt (48)

The procedure for **47** was followed using the amounts outlined below. Crude **41** (478 mg, 2.00 mmol) in dioxane (1.5 mL) and phosgene (4 mL, 6 g, 60 mmol) were stirred at 45 °C for 4 days. The solution was concentrated *in vacuo*, THF (4 mL) added, and the mixture was cooled to -78 °C. A solution of glycine *t*-butyl ester hydrochloride (**44**) (412 mg, 2.46 mmol) and *N*-methylpiperidine (0.25 mL, 2.1 mmol) in $CHCl_3$ (4 mL) at -78 °C was added, and the solution was allowed to warm to 20 °C overnight. *p*-Toluenesulfonic acid (0.53 g) in ethanol (4 mL) was added, the solution was concentrated *in vacuo* and the residue was separated on an MPLC column (RP8, Merck Lobar, 50 % CH_3OH/H_2O (0.1 % trifluoroacetic acid)) to give an oil (93.8 mg, 207 μmol, 10 % yield): IR (CH_2Cl_2 cast) 2995, 1742, 1674, 1203 cm^{-1}; ^1H NMR (360 MHz, CD_3OD) δ 7.16-7.36 (m, 5H, Ar$\underline{H}$), 3.92 (d, 1H, J=17.4 Hz, NC$\underline{H}$H), 3.84 (s, 2H, C$\underline{H}_2$Ph), 3.81 (d, 1H, J=17.5 Hz, NCH$\underline{H}$), 3.11 (d, 1H, J=14.4 Hz, C$\underline{H}$HSBn), 3.00 (d, 1H, J=14.4 Hz, CH$\underline{H}$SBn), 1.64 (s, 3H, NCC$\underline{H}_3$), 1.45 (s, 9H, C(C$\underline{H}_3$)$_3$); exact mass 338.1664 (338.1664 calcd. for $C_{17}H_{26}N_2O_3S$, M-$C_2HF_3O_2$); Anal. Calcd. for $C_{19}H_{27}F_3N_2O_5S$: C, 50.43; H, 6.01; N, 6.19. Found: C, 49.91; H, 5.97; N, 6.31.

α-Benzyl *N*-Carbobenzyloxy-(*S*)-glutamate (52)

The literature procedure[103] was followed with the amounts outlined below. Compound **50** (350. mg, 1.48 mmol) in THF (3 mL) was stirred with benzyl chloroformate (0.5 mL, 0.6 g, 4 mmol). A carbonate buffer (6.5 mL, 1 M $NaHCO_3$ and 1 M Na_2CO_3, pH 10) was added. After 1 h the solution was acidified to pH 1 (3M HCl) and extracted with EtOAc (3 X 10 mL). The mixture was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography ($CHCl_3$:CH_3OH 19:1) gave the known **52** as a colourless oil (19 mg, 51 μmol, 3 % yield): IR ($CHCl_3$ cast) 2980, 1797, 1748, 1721, 1303 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20-7.40 (m, 10H, Ar$\underline{H}$), 5.23 (s, 2H, ester C$\underline{H}_2$), 5.13 (s, 2H, carbamate C$\underline{H}_2$), 4.71 (dd, 1H, J=3.0, 8.0 Hz, C$\underline{H}$), 2.20-2.70 (m, 3H, CHC$\underline{H}$HC$\underline{H}_2$), 1.95-2.10 (m, 1H, CHCH$\underline{H}$CH$_2$); exact mass 353.1256 (353.1263 calcd. for $C_{20}H_{19}NO_5$).

(*S*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidinepropanoic Acid (54)

The literature procedure[50, 51] was followed using the amounts outlined below. Compound **53** (25.3 g, 90.1 mmol) was heated to reflux with benzene (700 mL), $(CH_2O)_n$ (4.96 g, 165 mmol) and *p*-toluenesulfonic acid (1.06 g, 6.20 mmol) in a Dean Stark apparatus for 6 h. The solution was washed with H_2O (700 mL) and extracted with $NaHCO_3$ (5 %, 700 mL). The aqueous phase was acidified to pH 1 (6 M HCl), and extracted with EtOAc (700 mL) The extracts were washed with H_2O (700 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give the known **54** as a colourless oil (26.1 g, 89.0 mmol, 99 % yield). IR ($CHCl_3$ cast) 2960, 1801, 1713, 1415 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.10 (s, 1H, COO$\underline{H}$), 7.30-7.40 (s, 5H, Ar$\underline{H}$), 5.55 (d, 1H, J=4.0 Hz, C$\underline{H}$HN), 5.23 (d, 1H, J=4.0 Hz, CH$\underline{H}$N), 5.18 (s, 2H, C$\underline{H}_2$Ph), 4.41 (t, 1H, J=6.0 Hz, 4-C$\underline{H}$), 2.44-2.58 (m, 2H, C$\underline{H}_2$COOH), 2.10-2.44 (m, 2H, 3-C$\underline{H}_2$); exact mass 293.0893 (293.0899 calcd. for $C_{14}H_{15}NO_6$).

(*S*)-3-(Benzyloxycarbonyl)-5-oxo-4-oxazolidinepropanoyl Chloride (55)

The literature procedure[50, 51] was followed using the amounts outlined below. Compound **54** (15.8 g, 53.9 mmol) was dissolved in benzene (60 mL) at 0 °C and phosphorous pentachloride (11.3 g, 54.0 mmol) was added. After 90 min the solution was concentrated *in vacuo*, $PhCH_3$ (25 mL) was added, and the solution was concentrated *in vacuo*. The residue was redissolved in $PhCH_3$ (25 mL) and the solution was concentrated *in vacuo* to give the known **55** as crystals (13.2 g, 42.3 mmol, 78 % yield): mp 50-65 °C (lit[50] mp 76-78 °C); IR (KBr disk) 3350, 1800, 1789, 1689 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38 (s, 5H, Ar$\underline{H}$), 5.40 (s, 1H, C$\underline{H}$HN), 5.18-5.24 (m, 3H, CH$\underline{H}$N & C$\underline{H}_2$Ph), 4.36 (t, 1H, J=6.0 Hz, 4-C$\underline{H}$), 3.06 (t, 2H, J=7.0 Hz, C$\underline{H}_2$COOH), 2.15-2.40 (m, 2H, 3-C$\underline{H}_2$); exact mass 275.0787 (275.0794 calcd. for $C_{14}H_{13}NO_5$).

Ethyl (*S*)-3-[(Benzyloxycarbonyl)-5-oxo-4-oxazolidine]propanoylglycinate (57) and Ethyl (*S*)-3-[(Benzyloxycarbonyl)-5-oxo-4-oxazolidine]propanoate (58)

To a solution of **55** (290 mg, 0.99 mmol) in THF (2 mL) at 0 °C was added a solution of glycine ethyl ester hydrochloride (**56**) (145 mg, 1.04 mmol), $CHCl_3$ (2 mL), THF (0.5 mL), and triethylamine (0.13 mL, 94 mg, 0.93 mmol). After 24 h, the solution was concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 1:2) gave first **58** as a colourless oil (60 mg, 0.2 mmol, 19 % yield) and then **57** as a colourless oil (60 mg, 0.2 mmol, 16 % yield). For **58**: IR ($CHCl_3$ cast) 2995, 1802, 1727, 1415 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.30-7.40 (m, 5H, Ar$\underline{H}$), 5.54 (d, 1H, J=4.5 Hz, ring C$\underline{H}$HN), 5.15-5.25 (d, 1H, J=4.5 Hz, ring CH$\underline{H}$N overlapping with s, 2H, C$\underline{H}_2$Ph), 4.38 (t, 1H, J=6.0 Hz, C$\underline{H}$N), 4.10 (q, 2H, J=7.0 Hz, C$\underline{H}_2$$CH_3$), 2.10-2.50 (m, 4H, C$\underline{H}_2C\underline{H}_2$), 1.24 (t, 3H, J=7.0 Hz, C$\underline{H}_3$); exact mass 321.1215 (321.1212 calcd. for $C_{16}H_{19}NO_6$); Anal. Calcd. for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.64; H, 6.14; N, 4.11.

For **57**: IR ($CHCl_3$ cast) 3380, 2940, 1800, 1718, 1415 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.20-7.50 (m, 5H, Ar$\underline{H}$), 5.53 (s, 1H, ring C$\underline{H}$HN), 5.23 (d, 1H, J=4.5 Hz, ring CH$\underline{H}$N), 5.20 (s, 2H, C$\underline{H}_2$Ph), 4.43 (dd, 1H, J=6.4, 10.8 Hz, C$\underline{H}$N), 4.20 (q, 2H, J=7.2 Hz, C$\underline{H}_2$$CH_3$), 3.97 (s, 2H, C$\underline{H}_2$NH), 2.39 (br. s, 2H, C$\underline{H}_2$CON), 2.25 (m, 2H, C$\underline{H}_2$CH); exact mass 378.1425 (378.1427 calcd. for $C_{18}H_{22}N_2O_7$).

N-Aminocamphorimide (60)

The literature procedure[70] was followed. To a solution of **62** (2.01 g, 11.0 mmol) in EtOH (95 %, 50 mL) was added hydrazine (0.71 mL, 22 mmol). After 5 min the solution was concentrated *in vacuo* and cooled to 0 °C for 1 day. The mixture was heated to 120 °C for 2 h, then 70 °C for 7.5 h and kept at 0 °C for 24 h. The mixture was recrystallized from EtOH/hexanes to give colourless crystals (0.27 g, 1.4 mmol, 12 % yield): mp 158-159 °C (lit[70] mp 156 °C); IR ($CHCl_3$ cast) 2967, 1725, 1669, 1044 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.71 (br. s, 2H, $N\underline{H}_2$), 2.78 (d, 1H, J=6.9 Hz, C-5$\underline{H}$), 2.24 (m, 1H, C-6$\underline{H}$H), 1.96 (m, 2H, C-7$\underline{H}_2$), 1.83 (m, 1H, C-6H$\underline{H}$), 1.24 (s, 3H, $C\underline{H}_3$), 0.98 (s, 3H, $C\underline{H}_3$), 0.97 (s, 3H, $C\underline{H}_3$); exact mass 196.1207 (196.1206 calcd. for $C_{10}H_{16}N_2O_2$); Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.36; H, 8.01; N, 14.20.

(1*R*,2*S*)-Camphoric Anhydride (62)

The literature procedure[131] was followed. A solution of (1*R*,3*S*)-(+)-camphoric acid (**61**) (10.0 g, 45.0 mmol), acetic anhydride (30.0 mL, 317 mmol) and acetyl chloride (60.0 mL, 844 mmol) was heated to reflux for 1.5 h, and then cooled to 20 °C. The mixture was concentrated *in vacuo* until crystals began to form and was then filtered to give the known **62** as colourless crystals (4.69 g, 25.7 mmol, 57 % yield): mp 225.5-226.0 °C (lit[131] mp 222-223 °C); IR ($CHCl_3$ cast) 3330, 2840, 1803, 1767 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.84 (d, 1H, J=6.6 Hz, C-5$\underline{H}$), 1.86-2.36 (m, 4H, C-6$\underline{H}_2$ & C-7$\underline{H}_2$), 1.27 (s, 3H, C-9$\underline{H}_3$), 1.10 (s, 3H, C-10$\underline{H}_3$), 1.00 (s, 3H, C-11$\underline{H}_3$); exact mass 138.1046 (138.1041 calcd. for $C_9H_{14}O$); MS (CI, NH_3) 183 (MH^+); Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.90; H, 8.03.

3-Amino-2-methylquinazolin-4(3H)-one (65)

The literature procedure[71] was followed. A solution of **67** (36.4 g, 165 mmol) in EtOH (95 %, 165 mL) and hydrazine (5.8 mL, 5.8 g, 180 mmol) was heated to reflux for 20 min and stored at 20 °C overnight. Filtration and recrystallization gave the known **65** as colourless crystals (23.8 g, 136 mmol, 82 % yield): mp 148-149 °C (lit[71] mp 146-148 °C); IR ($CHCl_3$ cast) 3200, 1664, 1604, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, 1H, J=1.4, 8.0 Hz, C-5$\underline{H}$), 7.74 (ddd, 1H, J=1.4, 7.7, 8.0 Hz, C-7$\underline{H}$), 7.64 (d, 1H, J=8.0 Hz, C-8$\underline{H}$), 7.45 (ddd, 1H, J=1.3, 7.7, 7.7 Hz, C-6$\underline{H}$), 4.90 (s, 2H, N$\underline{H}_2$), 2.70 (s, 3H, C$\underline{H}_3$); exact mass 175.0748 (175.0741 calcd. for $C_9H_9N_3O$); Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.56; H, 5.08; N, 23.96.

Ethyl *N*-(2-Carbomethoxyphenyl)acetimidate (67)

The literature procedure[71] was followed. A solution of **66** (40.0 g, 265. mmol) in triethyl orthoacetate (72.4 mL, 64.4 g, 397 mmol) was heated to reflux for 32.5 h and concentrated *in vacuo*. Two distillations gave the known **67** as a colourless liquid (36.2 g, 164 mmol, 62 % yield): bp 92 °C, 0.1 torr (lit[71] bp 80-84 °C, 0.25 torr); IR ($CHCl_3$ cast) 2990, 1728, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, 1H, J=1.5, 8.0 Hz, C-3$\underline{H}$), 7.41 (ddd, 1H, J=1.7, 7.7, 7.9 Hz, C-5$\underline{H}$), 7.06 (ddd, 1H, J=1.5, 7.5, 7.9 Hz, C-4$\underline{H}$), 6.75 (dd, 1H, J=1.0, 7.9 Hz, C-6$\underline{H}$), 4.26 (q, 2H, J=7.1 Hz, C$\underline{H}_2$CH$_3$), 3.82 (s, 3H, C$\underline{H}_3$), 1.75 (s, 3H, CC$\underline{H}_3$), 1.36 (t, 3H, J=7.1 Hz, C$\underline{H}_3$CH$_2$); exact mass 221.1054 (221.1047 calcd. for $C_{12}H_{15}NO_3$); Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.00; H, 6.82; N, 6.79.

Methyl *N*-(2'-Methylquinazolin-4'(3'H)onyl)aziridine-1-carboxylate (68)

The literature procedure[67] was followed with the modifications outlined below. To a solution of **65** (210 mg, 1.2 mmol), dichloromethane (3 mL), and methyl acrylate (**63**) (0.9 mL, 1 mmol) was added $Pb(OAc)_4$ of 95 % purity (0.58 g, 1.2 mmol) in portions over 15 min. The mixture was filtered and concentrated *in vacuo*. Flash chromatography ($CHCl_3$:CH_3OH 98:2) gave the known **68** as crystals (30 mg, 0.12 mmol, 12 % yield): mp 108-109.5 °C; IR (CH_2Cl_2 cast) 2930, 1745, 1678, 1597 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.19 (dd, 1H, J=1.4, 8.0 Hz, C-5'$\underline{H}$), 7.71 (m, 1H, C-7'$\underline{H}$), 7.59 (d, 1H, J=8.0 Hz, C-8'$\underline{H}$), 7.44 (m, 1H, C-6'$\underline{H}$), 3.88 (s, 3H, $C\underline{H}_3$), 3.51 (dd, 1H, J=5.2, 7.9 Hz, $C\underline{H}CH_2$), 3.04 (dd, 1H, J=1.2, 7.9 Hz, $C\underline{H}H$), 3.01 (dd, 1H, J=1.5, 5.2 Hz, $CH\underline{H}$), 2.76 (s, 3H, $CC\underline{H}_3$); exact mass 259.0953 (259.0951 calcd. for $C_{13}H_{13}N_3O_3$).

1-Amino-4,5-diphenyloxazolidin-2-one (77)

The literature procedure[73] for generation of analogous compounds was modified. To **76** (0.15 g, 1.1 mmol) and **74** (238 mg, 1.00 mmol) in DMF (3 mL) was added triethylamine (0.14 mL, 0.10 g, 1.0 mmol), and the mixture was stirred in the dark for 1 h. H_2O (15 mL) was added, the mixture was extracted with EtOAc (3 X 5 mL) and the organic phase was concentrated *in vacuo*. TFA (1.5 mL) was added and the solution was concentrated *in vacuo*. Flash chromatography ($CHCl_3$:CH_3OH 99:1) gave a light yellow oil (3.7 mg, 10. µmol, 1 % yield). IR ($CHCl_3$ cast) 3360, 1754 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.20-7.60 (m, 10H, Ar$\underline{H}$), 4.23 (s, 2H, $N\underline{H}_2$); exact mass 252.0902 (252.0899 calcd. for $C_{15}H_{12}N_2O_2$).

Benzaldehyde Benzyloxycarbonylhydrazone (80)

The literature procedure[132] was followed with the modifications outlined below. A solution of benzaldehyde (7.69 g, 72.5 mmol) in Et_2O (20 mL) at 0 °C was added slowly to hydrazine (4.65 g, 0.145 mmol) in Et_2O (13 mL) during 1.5 h. After 3h the ether layer was separated and washed with ice cold H_2O (35 mL). The organic layer was dried with Na_2SO_4 and filtered. Solid $NaHCO_3$ (7.3 g, 87 mmol) was added at 0 °C and then benzyloxycarbonyl chloride (10.3 mL, 12.4 g, 72.5 mmol) was slowly added. After 30 min a yellow precipitate was filtered. The residue was dissolved in acetone, and the solution was concentrated *in vacuo*. The residue was recrystallized from $CHCl_3$/hexanes to give the known **80** as a colourless solid (2.90 g, 11.4 mmol, 16 % yield): mp 140.5-141.5 °C (lit[132] mp 142 °C); IR ($CHCl_3$ cast) 3200, 3040, 1716, 1699, 1247 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.35 (br. s, 1H, N$\underline{H}$), 7.83 (br. s, 1H, C$\underline{H}$), 7.30-7.70 (m, 10H, Ar$\underline{H}$), 5.25 (s, 2H, C$\underline{H}_2$); exact mass 254.1055 (254.1050 calcd. for $C_{15}H_{14}N_2O_2$); Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 70.84; H, 5.75; N, 10.88.

Benzaldehyde Dibenzyloxycarbonylhydrazone (81)

The literature procedure[74] was followed with the modifications outlined below. To a 0 °C solution of **80** (1.00 g, 3.94 mmol) in DMF (16 mL) was added NaH of 50 % purity (0.26 g, 5.3 mmol). After hydrogen evolution ceased (10 min), the solution was cooled to -20 °C, a solution of carbobenzyloxy chloride (1.2 mL, 1.4 g, 8.4 mmol) in $PhCH_3$ (1.5 mL) was added, and the mixture was stirred at 0 °C for 2 h. The reaction mixture was poured on ice water (150 mL), the precipitate was filtered and recrystallized from 1-propanol to give the known **81** as crystals (1.12 g, 2.89 mmol, 73 % yield): mp 74-74.5 °C (lit[74] mp 78 °C); IR ($CHCl_3$ cast) 3040, 1769, 1750, 1268 cm^{-1}; 1H NMR (360 MHz, $CDCl_3$) δ 8.32 (s, 1H, C$\underline{H}$N), 7.30-7.80 (m, 15H, Ar$\underline{H}$), 5.30 (s, 4H, 2 X C$\underline{H}_2$); exact mass

388.1418 (388.1413 calcd. for $C_{23}H_{20}N_2O_4$); Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.24; H, 5.17; N, 6.88.

Carbohydrazide (82)

The literature procedure[75] was followed. To diethyl carbonate (**83**) (353 g, 2.99 mol) was added hydrazine hydrate (318 mL, 328 g, 6.56 mol) and the mixture was stirred for 10 min at 20 °C. Fractional distillation and trituration with EtOH gave the known **82** as a colourless solid (20.4 g, 226 mmol, 7 % yield): mp 163-165 °C (lit[75] mp 153-154 °C); IR (KBr disk) 3280, 1719, 1660, 1285 cm^{-1}; exact mass 90.0544 (90.0542 calcd. for CH_6N_4O).

(E)-Methyl Cinnamate (85)

The literature procedure[133] for generation of analogous compounds was adapted. To a solution of cinnamoyl chloride (1.50 g, 9.00 mmol) in CH_3OH (10 mL) was added NaOMe (0.49 g, 9.1 mmol), and the mixture was stirred at 20 °C. After 20 min the mixture was filtered and concentrated *in vacuo*. The residue was bulb to bulb distilled to give the known **85** as a colourless oil which crystallized at 0 °C (0.93 g, 5.7 mmol, 64 % yield): mp 33-33.5 °C (lit[122] mp 36 °C); IR (CH_2Cl_2 cast) 3000, 1714, 1640, 1316 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 1H, J=16.1 Hz, C$\underline{H}$Ph), 7.49 (m, 2H, Ar$\underline{H}$), 7.35 (m, 3H, Ar$\underline{H}$), 6.43 (d, 1H, J=16.1 Hz, C$\underline{H}$CO), 3.78 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.16 ($\underline{C}$=O), 144.64 ($\underline{C}$HPh), 134.16 (Ar$\underline{C}$), 130.09 (Ar$\underline{C}$), 128.68 (Ar$\underline{C}$), 127.87 (Ar$\underline{C}$), 117.60 ($\underline{C}HCO_2$), 51.44 (O$\underline{C}H_3$); exact mass 162.0679 (162.0680 calcd. for $C_{10}H_{10}O_2$); Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21; Found: C, 73.84; H, 6.36.

Methyl 3-Phenyl-*N*-phthalimidoaziridine-2-carboxylate (86)

The literature procedure[61] for generation of analogous compounds was followed. To a solution of **85** (0.93 g, 5.7 mmol) in dichloromethane (5 mL) was added *N*-aminophthalimide (**84**) (1.05 g, 6.48 mmol) under Ar. To the resulting suspension was sprinkled in $Pb(OAc)_4$ of 95 % purity (2.95 g, 6.32 mmol) in portions over 7 min. Additional dichloromethane (5 mL) was added. The mixture was stirred for 15 min, filtered, and concentrated *in vacuo*. The residue was recrystallized from CH_3OH to give the known **86** as a solid (0.89 g, 2.8 mmol, 48 % yield): mp 138.5-140 °C; IR ($CHCl_3$ cast) 2980, 1720, 1376 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.40-8.00 (m, 9H, Ar$\underline{H}$), 4.57 (d, 1H, J=5 Hz, C$\underline{H}$Ph), 3.95 (s, 3H, C$\underline{H}_3$), 3.70 (d, 1H, J=5 Hz, C$\underline{H}$CO); exact mass 322.0953 (322.0953 calcd. for $C_{18}H_{14}N_2O_4$).

Ethyl (2*RS*)-*N*-Phthalimidoaziridine-2-carboxylate (88)

The literature procedure[61] was followed using the amounts outlined below. *N*-Aminophthalimide (**84**) (3.32 g, 20.5 mmol), $CHCl_3$ (50 mL), ethyl acrylate (**80**) (12.0 mL, 11.0 mg, 111 mmol), $Pb(OAc)_4$ of 95 % purity (10.6 g, 22.7 mmol). Recrystallization from EtOH gave the known **88** as crystals (1.79 g, 6.88 mmol, 34 % yield): mp 160-161 °C (lit[61] mp 160 °C); IR ($CHCl_3$ cast) 3120, 1746, 1717, 1361 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.65-7.85 (m, 4H, Pht$\underline{H}$), 4.10-4.40 (m, 2H, C$\underline{H}_2$CH$_3$ major & C$\underline{H}_2$CH$_3$ minor), 3.24 (m, 0.2H, C$\underline{H}(\alpha)$ minor), 3.17 (dd, 0.8H, J=5.5, 7.6 Hz, C$\underline{H}(\alpha)$ major), 2.87 (dd, 1H, J=1.8, 5.5 Hz, C$\underline{H}$H(β)), 2.83 (dd, 1H, J=1.8, 7.6 Hz, CH$\underline{H}$(β)), 1.44 (dd, 2.5H, J=6.9, 7.5 Hz, C$\underline{H}_3$ major), 1.25 (dd, 0.5H, J=6.9, 6.9 Hz, C$\underline{H}_3$); exact mass 260.0799 (260.0797 calcd. for $C_{13}H_{12}N_2O_4$); Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76; Found: C, 59.86; H, 4.34; N, 10.74.

Methyl (2*RS*)-*N*-Phthalimidoaziridine-2-carboxylate (89)

The literature procedure[61] was followed using the amounts outlined below *N*-Aminophthalimide (**84**) (0.33 g, 2.0 mmol), dichloromethane (5 mL), methyl acrylate (**63**) (0.90 mL, 860 mg, 10 mmol), $Pb(OAc)_4$ of 95 % purity (0.98 g, 2.2 mmol). Recrystallization from EtOH gave the known **89** as colourless crystals (0.26 g, 1.1 mmol, 51 % yield): mp 166-167.5 °C (lit[61] mp 172 °C); IR ($CHCl_3$ cast) 2960, 1769, 1721, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.85 (m, 4H, Ar$\underline{H}$), 3.86 (s, 2.6H, $C\underline{H}_3$), 3.72 (s, 0.4H, $C\underline{H}_3$), 3.21 (dd, 1H, J=5.2, 7.9 Hz, $C\underline{H}$), 2.88 (dd, 1H, J=1.7, 5.2 Hz, $C\underline{H}H$), 2.86 (dd, 1H, J=1.8, 7.9 Hz, $CH\underline{H}$); exact mass 246.0637 (246.0640 calcd. for $C_{12}H_{10}N_2O_4$); Anal. Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38; Found: C, 58.36; H, 3.99; N, 11.30.

Methyl *N*-Phthalimidoaziridine-2-carboxylate (89) From 101.

The literature procedure[61] was followed. To a solution of *N*-aminophthalimide (**84**) (185 mg, 1.10 mmol) in dichloromethane (5 mL) was added methyl *O*-acryloylmandelate (**101**) (0.27 g, 1.2 mmol) and $Pb(OAc)_4$ of 95 % purity (0.48 g, 1.1 mmol) was sprinkled in over 10 min. After 30 min the mixture was filtered and concentrated *in vacuo*. Flash chromatography ($CHCl_3$:CH_3OH 99:1) and recrystallization from $CHCl_3$/CH_3OH gave colourless crystals (25.5 mg, 104 µmol, 10 % yield): mp 166-167.5 °C (lit[61] mp 166-167.5 °C); $[\alpha]_D$= +4° (c=0.55 EtOH); IR ($CHCl_3$ cast) 2940, 1745, 1712 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.70-7.85 (m, 4H, Ar$\underline{H}$), 3.87 & 3.72 (2 X s, 3H, $C\underline{H}_3$), 3.21 (dd, 1H, J=5.2, 5.6 Hz, $C\underline{H}$), 2.86 (m, 2H, $C\underline{H}_2$); exact mass 246.0641 (246.0641 calcd. for $C_{12}H_{10}N_2O_4$). A 9 mol % solution of $Eu(HFC)_3$ in $CDCl_3$ showed the following: ^1H NMR (200 MHz, $CDCl_3$) δ 4.40 (s, 1.35H, $C\underline{H}_3$), 4.20 (s, 1.35H, $C\underline{H}_3$), 3.75 (s, 0.15H, $C\underline{H}_3$), 3.76 (s, 0.15H, $C\underline{H}_3$).

Methyl (2*RS*)-2-(Phenylmethylthio)-3-[N-phthalimido(amino)]propanoate (90)

The literature procedure[34] for generation of analogous compounds was adapted. To a solution of **89** (248 mg, 1.01 mmol) in DMF (7 mL) at -50 °C was added sodium benzylthiolate (1.2 mL, 8.1 M, 1.1 mmol) dropwise over 2 min. After 50 min, H_3PO_4 (20 mL, 0.05 M) was added. The mixture was extracted with EtOAc (3 x 25 mL), dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 2:1) gave a colourless solid (170 mg, 0.46 mmol, 45 % yield): mp 93.5-94 °C; IR ($CHCl_3$ cast) 3300, 2970, 1785, 1723, 1395 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) 7.70-7.90 (m, 4H, PhtH), 7.10-7.35 (m, 5H, PhH), 4.97 (t, 1H, J=5.6 Hz, NH), 3.88 (s, 2H, CH_2Ph), 3.76 (s, 3H, CH_3) 3.50 (ddd, 1H, J=5.7, 8.7, 12.5 Hz, CHHN), 3.42 (dd, 1H, J=5.4, 8.7 Hz, CH), 3.18 (ddd, 1H, J=5.4, 5.7, 12.6 Hz, CHHN); exact mass 370.0993 (370.0987 calcd. for $C_{19}H_{18}N_2O_4S$); Anal. Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.30; H, 4.82; N, 7.49.

Ethyl (2*RS*)-2-Methylthio-3-[N-phthalimido(amino)]propanoate (93) and Ethyl (2*RS*)-3-Methylthio-2-[N-phthalimido(amino)]propanoate (94)

The literature procedure[81] for generation of analogous compounds was adapted. To a stirred solution of **88** (277.5 mg, 1.058 mmol) in dichloromethane (5 mL) and methanethiol (2.0 mL, 1.7 g, 36 mmol) at -45 °C was added boron trifluoride etherate (0.20 mL, 230 mg, 1.6 mmol). After 4 h the solution was warmed to -20 °C and stirred overnight. Flash chromatography (hexanes:EtOAc 1:1) gave an oil (0.18 g, 0.58 mmol, 55 % yield) as an unseparated mixture of the two regioisomers in a ratio of 1:1.6 for compounds **93**:**94**, respectively. Repeated MPLC (3 X) (Merck SiO_2, PF_{254}, hexanes:EtOAc 7:3) separated both isomers. For compound **93** (31.0 mg, 0.101 mmol, 9 % yield): IR ($CHCl_3$ cast) 3300, 2920, 1795, 1723, 1387 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70-7.90 (m, 4H, ArH), 5.04 (t, 1H, J=5.0 Hz, NH), 4.23 (q, 2H, J=7.0 Hz, CH_2CH_3), 3.48 (m, 2H, C-2$\underline{H}$ & C-3$\underline{H}$), 3.30 (ddd, 1H, J=7.0, 11.3 Hz, third J obscured, C-3$\underline{H}$), 2.20 (s, 3H, C$\underline{H}_3$S), 1.31 (t, 3H, J=7.0 Hz, C$\underline{H}_3$CH$_2$); exact mass 308.0830 (308.0830 calcd. for $C_{14}H_{16}N_2O_4S$).

For compound **94** (15.3 mg, 50.0 μmol, 5 % yield): IR (CHCl$_3$ cast) 3280, 2920, 1795, 1726, 1384 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.70-7.90 (m, 4H, Ar$\underline{H}$), 5.46 (br. s, 1H, N$\underline{H}$), 4.22 (dq, 2H, J=1.0, 7.0 Hz, C$\underline{H}_2$CH$_3$), 4.07 (br. s, 1H, C-2$\underline{H}$), 3.00-2.92 (m, 2H, C-3$\underline{H}_2$), 2.26 (s, 3H, C$\underline{H}_3$S), 1.26 (t, 3H, J=7.0 Hz, C$\underline{H}_3$CHH); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.49 ($\underline{C}$O$_2$), 166.30 ($\underline{C}$ON), 134.36 (Ar$\underline{C}$), 130.13 (Ar$\underline{C}$), 123.52 (Ar$\underline{C}$), 61.77 ($\underline{C}$H$_2$CH$_3$), 60.46 ($\underline{C}$(α)), 34.60 ($\underline{C}$H$_3$CH$_2$) 15.60 ($\underline{C}$(β)), 14.00 ($\underline{C}$H$_3$S); exact mass 308.0830 (308.0830 calcd. for $C_{14}H_{16}N_2O_4S$).

Methyl (2*R*,3*S*)- and (2*S*,3*R*)-3-(*p*-Methoxyphenyl)methylthio-3-phenyl-2-[N-phthalimido(amino)]propanoate (97)

The literature procedure[81] for generation of analogous compounds was adapted. To a solution of **86** (0.24 g, 0.75 mmol) in dichloromethane (5 mL) at -78 °C was added *p*-methoxybenzylthiol (**90**) (0.94 g, 6.1 mmol) and boron trifluoride etherate (0.43 mL, 0.48 g, 3.4 mmol). After 15 min, sodium phosphate buffer (pH 7, 10 mL) and H$_2$O (10 mL) was added and the layers were separated. The aqueous phase was washed with dichloromethane (2 X 10 mL) and the pooled organic phases were dried with Na$_2$SO$_4$, filtered and concentrated *in vacuo*. Flash chromatography gave an oil (0.21 g, 0.44 mmol, 59 % yield): IR (CHCl$_3$ cast) 2960, 1721, 1510 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65-7.80 (m, 4H, Pht$\underline{H}$), 7.30-7.50 (m, 5H, Ph$\underline{H}$), 7.12 (ddd, 2H, J=1.7, 3.4, 8.4 Hz, ArC$\underline{H}$ ortho to CH$_2$S), 6.80 (ddd, 2H, J=1.7, 3.4, 8.4 Hz, ArC$\underline{H}$ meta to CH$_2$S), 4.72 (br. s, 1H, N$\underline{H}$), 4.27 (d, 1H, J=9.7 Hz, C$\underline{H}$Ph), 4.08 (d, 1H, J=9.7 Hz, C$\underline{H}$CO), 3.78 (s, 3H, C$\underline{H}_3$O), 3.72 (s, 3H, C$\underline{H}_3$O), 3.61 (d, 1H, J=13.2 Hz, C$\underline{H}$HS), 3.45 (d, 1H, J=13.2 Hz, CH$\underline{H}$S); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.21 ($\underline{C}$O$_2$), 165.64 ($\underline{C}$ON), 158.63 (ArC), 137.29 (ArC), 134.19 (ArC), 130.04 (ArC), 129.82 (ArC), 128.93 (ArC), 126.93 (ArC), 126.68 (ArC), 125.11 (ArC), 123.33 (ArC), 113.72 (ArC), 65.93 (CHPh), 55.15 (CH_3OAr), 52.43 (OCH_3), 48.43 (CHCO), 34.98 (CH_2S); For ^1H-^{13}C Hetcor and BIRDTRAP NMR data see Figure 2; exact mass 322.0953 (322.0954 calcd. for $C_{18}H_{14}N_2O_4$, M^+-$C_8H_{10}OS$); MS (CI, NH_3) 477 (MH^+); Anal. Calcd. for $C_{26}H_{24}N_2O_5S$: C, 65.53; H, 5.08; N, 5.88; Found: C, 65.10; H, 5.11; N, 5.88.

Methyl (2*R*,3*S*)-3-Methylthio-3-phenyl-2-[N-phthalimido(amino)]propanoate and Methyl (2*S*,3*R*)-3-Methylthio-3-phenyl-2-[N-phthalimido(amino)]-propanoate (98)

The literature procedure[81] for generation of analogous compounds was adapted. To a solution of **86** (0.10 g, 0.31 mmol) in dichloromethane (2 mL) at -78 °C was added methanethiol (0.27 g, 5.6 mmol) and boron trifluoride etherate (0.18 mL, 0.20 g, 1.4 mmol). After 50 min, sodium phosphate buffer (pH 7, 10 mL) and H_2O (10 mL) was added, the layers were separated and the aqueous phase was washed with dichloromethane (10 mL). The pooled organic phases were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was crystallized from CH_3OH to give colourless crystals (0.10 g, 0.27 mmol, 87 % yield): mp 126-126.5 °C; IR ($CHCl_3$ cast) 3280, 3010, 1790, 1728, 1384 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.85 (m, 4H, PhtH), 7.25-7.55 (m, 5H, ArH), 4.80 (br. s, 1H, NH), 4.36 (d, 1H, J=9.9 Hz, CHPh), 4.16 (d, 1H, J=9.9 Hz, CHCO), 3.79 (s, 3H, CH_3), 1.96 (s, 3H, SCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.44 (CO_2), 165.68 (CON), 136.83 (ArC), 134.23 (ArC), 129.84 (ArC), 128.67 (ArC), 128.57 (ArC), 128.06 (ArC), 123.35 (ArC), 65.52 (CHPh), 52.51 (OCH_3), 50.64 (CHCO), 14.11 (SCH_3); exact mass 370.0975 (370.0987 calcd. for $C_{19}H_{18}N_2O_4S$); Anal. Calcd. for $C_{19}H_{18}N_2O_4S$: C, 61.61; H, 4.90; N, 7.56; Found: C, 61.48; H, 4.47; N, 7.59.

(1*R*,2*S*)-2'-Phenylcyclohexyl Propenoate (104) and (1*R*,2*S*)-2'-Phenylcyclohexyl 3-Chloropropanoate (105)

The literature procedure[134] for generation of analogous compounds was adapted. Freshly distilled acryloyl chloride (0.86 mL, 0.96 g, 9.9 mmol) was heated to reflux with a solution of **103** (1.74 g, 10.0 mmol) in THF (10 mL) for 6 h. The solution was concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 6:1) gave a colourless oil (0.97 g) as an unseparated mixture (1:1.4) of **104** and **105**, respectively: IR ($CHCl_3$ cast) 2935, 2858, 1723, 1196 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) for **104**: δ 7.10-7.30 (m, 5H, Ar$\underline{H}$), 6.16 (dd, 1H, J=2.0, 14.4 Hz, C$\underline{H}$ vinyl), 5.88 (dd, 1H, J=7.2, 14.4 Hz, C$\underline{H}$ vinyl), 5.64 (dd, 1H, J=7.2, 14.4 Hz, C$\underline{H}$ vinyl), 5.00 (m, 1H, C$\underline{H}$O), 1.30-2.70 (m, 9H, C$\underline{H}$ cyclohexyl); for **105**: δ 3.47 (t, 2.8H, J=7.0 Hz, $C\underline{H}_2Cl$), 2.49 (t, 2.8H, J=7.0 Hz, $C\underline{H}_2CO$); exact mass for **104**: 230.1306 (230.1306 calcd. for $C_{15}H_{18}O_2$, M^+); for **105**: 230.1306 (230.1306 calcd. for $C_{15}H_{18}O_2$, M^+-HCl); MS (CI, NH_3) for **104**: 248 (MNH_4^+), 231 (MH^+); for **105**: 284 (calcd. for ^{35}Cl: MNH_4^+), 286 (calcd. for ^{37}Cl: MNH_4^+).

Methyl (*S*)-3-Phenyl-2-[(propenoyl)oxy]propanoate (101)

The literature procedure[134] for generation of analogous compounds was adapted. Freshly distilled acryloyl chloride (1.8 mL, 2.0 g, 20. mmol) was heated to reflux with a solution of **100** (3.51 g, 21.1 mmol) in acetonitrile (20 mL) for 9.5 h. The solution was concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 5:1) gave a colourless oil (1.57 g, 7.13 mmol, 33 % yield). IR ($CHCl_3$ cast) 2960, 1758, 1731, 1170 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35-7.55 (m, 5H, Ar$\underline{H}$), 6.54 (dd, 1H, J=1.5, 17.2 Hz, cis C$\underline{H}$H=CH), 6.25 (dd, 1H, J=10.2, 17.2 Hz, C$\underline{H}$=CHH), 6.01 (s, 1H, C$\underline{H}$O), 5.93 (dd, 1H, J=1.5, 10.3 Hz, trans CH$\underline{H}$=CH), 3.73 (s, 3H, $C\underline{H}_3$); exact mass 220.0753 (220.0732 calcd. for $C_{12}H_{12}O_4$); Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.13; H, 5.38.

(4*S*)-3-(2-Propenoyl)-4-(phenylmethyl)-2-oxazolidinone (108)

The literature procedure[83] was followed with the modifications outlined below. Methyl magnesium bromide (1.6 mL, 4.8 mmol) was added to a -20 °C solution of **107** (0.85 g, 4.8 mmol) in THF (40 mL). Acryloyl chloride was added (0.39 mL, 0.43 g, 4.8 mmol) and then saturated NH_4Cl (4 mL) was added. The mixture was extracted into Et_2O (200 mL) and washed with saturated NH_4Cl (200 mL). The layers were separated, and the organic phase was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:Et_2O 1:1) gave a colourless solid (0.75 g, 3.2 mmol, 67 % yield): mp 75-76 °C (lit[83] mp 84.5-86.5 °C); IR (CH_2Cl_2 cast) 3030, 1778, 1685, 1619 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.52 (dd, 1H, J=10.4, 17.0 Hz, $C\underline{H}CHH$), 7.20-7.40 (m, 5H, $Ar\underline{H}$), 6.61 (dd, 1H, J=1.8, 17.0 Hz, cis $C\underline{H}H{=}CH$), 5.93 (dd, 1H, J=1.8, 10.4 Hz, trans $CH\underline{H}{=}CH$), 4.74 (m, 1H, C-4$\underline{H}$), 4.22 (m, 2H, $C\underline{H}_2Ph$), 3.35 (dd, 1H, J=3.3, 13.4 Hz, $C\underline{H}HO$), 2.81 (dd, 1H, J=9.5, 13.4 Hz, $CH\underline{H}O$); exact mass 231.0893 (231.0891 calcd. for $C_{13}H_{13}NO_3$); Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.83; H, 5.61; N, 5.89.

(4*S*)-3-[(2*RS*)-2-(*N*-Phthalimidoaziridinyl)carbonyl]-4-(phenylmethyl)-2-oxazolidinone (109)

The literature procedure[61] for generation of analogous compounds was followed with the modifications outlined below: To a suspension of *N*-aminophthalimide (**84**) (109 mg, 0.672 mmol) and **108** (0.60 g, 2.6 mmol) in dichloromethane (5 mL) was added $Pb(OAc)_4$ of 95 % purity (0.31 g, 0.67 mmol) in portions at 20 °C over 10 min. After 15 min, the mixture was filtered and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 2:1) followed by flash chromatography again (hexanes:EtOAc 1:1) gave a colourless powder (20.6 mg, 52.7 µmol, 8 % yield) HPLC (µPorasil, hexanes:EtOAc 1:1) showed t_R=5.75, 6.65 min having areas on the UV trace (254 nm) of 51 % and 49 % respectively. mp 182-184 °C; IR ($CHCl_3$ cast) 1780, 1720, 1376 cm^{-1}; ^1H NMR (400

MHz, $CDCl_3$) δ 7.76 (m, 4H, PhtH), 7.20-7.40 (m, 5H, PhH), 4.80 (m, 1H, C-5H), 4.62 (dd, 1H, J=5.3, 7.8 Hz, CHCO), 4.37 (m, 1H, CHHPh), 4.26 (dd, 1H, J=2.5, 9.3 Hz, CHHPh), 3.34 (dd, 1H, J=3.0, 13.4 Hz, C-4HH), 3.11 (dd, 1H, J=1.5, 7.8 Hz, CHHN), 3.01 (dd, 1H, J=1.5, 5.3 Hz, CHHN), 2.82 (dd, 1H, J=9.8, 13.5 Hz, C-4HH); exact mass 391.1165 (391.1161 calcd. for $C_{21}H_{17}N_3O_5$); Anal. Calcd. for $C_{21}H_{17}N_3O_5$: C, 64.45; H, 4.38; N, 10.74. Found: C, 64.07; H, 4.28; N, 10.44.

4-Propenoyl-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (110)

The literature procedure[84] was followed using the amounts outlined below. Compound **115** (586 mg, 2.72 mmol) was dissolved in $PhCH_3$ (10 mL) and added to sodium hydride of 50 % purity in mineral oil (192 mg, 4.01 mmol) in $PhCH_3$ (2 mL). Acryloyl chloride (0.5 mL, 50 mg, 5 mmol) was added and stirred overnight. H_2O (4 mL) was added, the layers were separated, and the aqueous phase was washed with $CHCl_3$ (5 X 10 mL). The pooled organic layers were dried with Na_2SO_4, filtered and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 4:1) gave the known **110** as a colourless powder (0.19 g, 0.70 mmol, 26 % yield): mp 199-200 °C; (lit[84] mp 196-197 °C); IR ($CHCl_3$ cast) 2960, 1675, 1329 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.88 (dd, 1H, J=10.8, 16.2 Hz, CH vinyl), 6.41 (dd, 1H, J=2.0, 16.2 Hz, CH vinyl), 5.87 (dd, 1H, J=2.0, 10.8 Hz, CH vinyl), 3.95 (dd, 1H, J=5.4, 7.2 Hz, CHN), 3.53 (d, 1H, J=13.8 Hz, $CHHSO_2$), 3.46 (d, 1H, J=13.8 Hz, $CHHSO_2$), 1.85-2.20 (m, 5H, camphor ring protons), 1.30-1.45 (m, 2H, CH_2CHN), 1.17 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); exact mass 269.1083 (269.1086 calcd. for $C_{13}H_{19}NO_3S$); Anal. Calcd. for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20; Found: C, 57.96; H, 6.96; N, 5.11.

4-Propenoyl-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decane-5,5-dioxide (110) From 141.

The literature procedure[34] was modified. To a stirred solution of **141** (13.4 mg, 24.1 µmol) in DMF (0.1 mL) was added sodium benzylthiolate (0.06 mL, 0.9 M, 50 µmol) and the mixture was stirred for 21 h at 20 °C. H_2O (1 mL) was added, and the solution was extracted with hexanes (2 X 5 mL). The aqueous phase was acidified to pH $\leq$ 2.5 and extracted with CH_2Cl_2 (3 X 5 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was separated on an MPLC column (Merck SiO_2 PF_{254}, hexanes: EtOAc 2:1) to give the known **110** as a colourless powder (4.9 mg, 18 µmol, 73 % yield). The spectral properties were identical to those of authentic **110** prepared above.

D-Camphorsulfonimine (114)

The literature procedure[88, 89] was followed using the amounts outlined below. D-Camphorsulfonic acid (**111**) (47.2 g, 0.203 mol) was dissolved in thionyl chloride (60.0 mL, 97.9 g, 0.822 mmol) to generate **112**. To a solution of NH_4OH (450 mL) was added a solution of dichloromethane (450 mL) and the sulfonyl chloride **112** in two equal portions. The layers were separated, and the aqueous phase was washed with dichloromethane (2 X 100 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give the known D-camphorsulfonamide (**113**) as a colourless solid (42.8 g, 0.185 mol, 91 % yield) which was used without further purification: mp 133-134 °C (lit[88] mp 125-128 °C).

The literature procedure was followed using the amounts outlined below. Compound **113** (42.8 g, 0.185 mol) and Amberlyst XN-1010 ion exchange resin (5.09 g) were heated to reflux in $PhCH_3$ (500 mL) in a Dean and Stark apparatus. The mixture was cooled after 4 mL H_2O had been collected, and dichloromethane (200 mL) was added. The mixture was filtered, and the solid was rinsed with dichloromethane (75 mL). The filtrate was concentrated *in vacuo*, and the residue was recrystallized from EtOH to give the known **114** as a colourless solid (29.0 g, 0.136 mol, 67 % yield): mp 229-230 °C (lit[88] mp 225-228 °C); IR ($CHCl_3$ cast) 3000, 1658, 1215, 760 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.28 (d, 1H, J=13.0 Hz, $C\underline{H}HSO_2$), 3.10 (d, 1H, J=13.0 Hz, $CH\underline{H}SO_2$), 2.60-2.75 (m, 1H, camphor ring proton), 1.45-2.20 (m, 6H, camphor ring protons), 1.18 (s, 3H, $C\underline{H}_3$), 1.03 (s, 3H, $C\underline{H}_3$); exact mass 213.0824 (213.0823 calcd.for $C_{10}H_{15}NO_2S$).

(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (D-2,10-Camphorsultam) (115)

The literature procedure[88] was followed using the amounts outlined below. Compound **114** (9.20 g, 43.1 mmol) was stirred with THF (250 mL) and $LiAlH_4$ (1.67 g, 43.1 mmol) for 24 h. HCl (6M, 200 mL) was added dropwise and the mixture was filtered through Celite. Chloroform (500 mL) was added and the layers were separated. The aqueous phase was washed with $CHCl_3$ and the pooled organic phases were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give a colourless solid. The residue was recrystallized from EtOH to give the known **115** as a colourless solid (3.42 g, 15.9 mmol, 37 % yield): mp 185-186 °C (lit[88] mp 183-184 °C); IR ($CHCl_3$ cast) 3295, 2967, 1137, 762 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.25 (br. s, 1H, $N\underline{H}$), 3.42 (dd, 1H, J=5.0, 8.0 Hz, $C\underline{H}N$), 3.16 (d, 1H, J=13.0 Hz, $C\underline{H}HSO_2$), 3.08 (d, 1H, J=13.0 Hz, $CH\underline{H}SO_2$), 1.80-2.05 (m, 5H, camphor ring protons), 1.25-1.55 (m, 2H, $C\underline{H}_2CHN$), 1.14 (s, 3H, $C\underline{H}_3$), 0.94 (s, 3H, $C\underline{H}_3$); exact mass 215.0977 (215.0979 calcd. for $C_{10}H_{17}NO_2S$);

Anal. Calcd. for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51; Found: C, 55.74; H, 8.06; N, 6.44.

(2*R*)-4-[2-(*N*-Phthalimidoaziridinyl)carbonyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decane-5,5-dioxide (116) and (2*S*)-4-[2-(*N*-Phthalimidoaziridinyl)carbonyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo-[5.2.1.0^{3,7}]decane-5,5-dioxide (117)

The literature procedure[61] for generation of analogous compounds was adapted. To a solution of **110** (1.19 g, 4.29 mmol) in dichloromethane (20 mL) was added *N*-aminophthalimide (**84**) (1.07 g, 6.60 mmol) under dry Ar. To the resulting suspension was sprinkled in $Pb(OAc)_4$ of 95 % purity (3.12 g, 6.69 mmol) in portions over 7 min. The mixture was stirred for 15 min, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 2:1) gave a colourless solid (1.40 g, 3.26 mmol, 76 % yield) as an 8:1 mixture of diastereomers according to ^{1}H NMR (78 % de). Recrystallization from $PhCH_3$/hexanes caused the major isomer **116** to precipitate. For **116**: mp 201-203 °C; $[\alpha]_D^{20}$ = -7° (c=0.271 g/100 mL); IR ($CHCl_3$ cast) 2960, 1785, 1770, 1721 cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) 7.73-7.98 (m, 4H, ArH), 3.95 (dd, 1H, J=4.9, 7.8 Hz, CHN), 3.83 (dd, 1H, J=5.5, 7.8 Hz, C-2'H), 3.63 (d, 1H, J=14.0 Hz, $CHHSO_2$), 3.49 (d, 1H, J=14.0 Hz, $CHHSO_2$), 3.02 (dd, 1H, J=1.6, 7.5 Hz, C-3'HH), 2.91 (dd, 1H, J=1.6, 5.5 Hz, C-3'HH), 2.31 (d, 1H, J=14.0 Hz, C-2HHCHN), 2.13 (dd, 1H, J=7.8, 14.0 Hz, C-2HHCHN), 1.94 (m, 3H, camphor ring protons), 1.34 (m, 5H, CH_3 & camphor ring protons), 1.02 (s, 3H, CH_3); exact mass 429.1350 (429.1358 calcd. for $C_{21}H_{23}N_3O_5S$); Anal. Calcd for $C_{21}H_{23}N_3O_5S$: C, 58.71; H, 5.40; N, 9.79. Found: C, 58.39; H, 5.32; N, 9.45. For **117** Characteristics: ^{1}H NMR (300MHz, $CDCl_3$) δ 3.21 (dd, 1H, J=1.6, 5.8 Hz, C-3'HH), 2.88 (dd, 1H, J=1.6, 4.5 Hz, C-3'HH). Remaining spectral properties were indistinguishable from those of **116**.

4-(E)-3'-Methylpropenoyl-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo-[5.2.1.$0^{3,7}$]decane-5,5-dioxide (122)

The literature procedure[135] was followed using the amounts outlined below. Compound **115** (609 mg, 2.83 mmol) was dissolved in $PhCH_3$ (10 mL) and added to sodium hydride (157 mg, 3.28 mmol) in $PhCH_3$ (2 mL). (E)-Crotonyl chloride (**118**) of 90 % purity (0.48 mL, 54 mg, 5.4 mmol) in $PhCH_3$ (8 mL) was added, and the mixture was stirred for 8 h. H_2O (4 mL) was added and the layers were separated. The aqueous phase was washed with $CHCl_3$ (3 X 5 mL). The pooled organic phases were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was recrystallized from CH_3OH to give the known **122** as a colourless solid (455 mg, 1.60 mmol, 57 % yield): IR ($CHCl_3$ cast) 2960, 1676, 1638, 1326 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.11 (dq, 1H, J=6.9, 14.9 Hz, C-3$\underline{H}$), 6.59 (dq, 1H, J=1.5, 14.9 Hz, C-2$\underline{H}$), 3.93 (dd, 1H, J=5.8, 6.8 Hz, C$\underline{H}$N), 3.52 (d, 1H, J=13.8 Hz, $C\underline{H}HSO_2$), 3.43 (d, 1H, J=13.8 Hz, $CH\underline{H}SO_2$), 1.93 (dd, 3H, J=7.0 Hz, $C\underline{H}_3CH$), 1.80-2.15 (m, 3H, camphor ring protons), 1.30-1.60 (m, 4H, camphor ring protons), 1.18 (s, 3H, $C\underline{H}_3$), 0.98 (s, 3H, $C\underline{H}_3$); exact mass 283.1239 (283.1242 calcd. for $C_{14}H_{21}NO_3S$); Anal. Calcd. for C, 59.34; H, 7.47; N, 4.94; Found: C, 59.26; H, 7.59; N, 4.89.

4-(E)-3'-Phenylpropenoyl-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (123)

The literature procedure[135] for generation of analogous compounds was followed using the amounts outlined below. Compound **115** (2.24 g, 10.4 mmol) was dissolved in $PhCH_3$ (50 mL) and added to sodium hydrdide (0.54 g, 11 mmol) in $PhCH_3$ (25 mL). Cinnamoyl chloride (2.03 g, 12.2 mmol) in $PhCH_3$ (25 mL) was added and the mixture was stirred for 3 h. H_2O (20 mL) was added and the layers were separated. The aqueous phase was washed with $CHCl_3$ (3 X 10 mL), and the pooled organic phases were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 4:1) gave a colourless

solid (3.38 g, 9.78 mmol, 94 % yield): mp 187.5-189 °C; IR ($CHCl_3$ cast) 2960, 1676, 1624, 1333 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 1H, J=15.5 Hz, C-2'H), 7.56-7.60 (m, 2H, ArH), 7.36-7.40 (m, 3H, ArH), 7.18 (d, 1H, J=15.5 Hz, C-3'H), 4.00 (dd, 1H, J=4.9, 7.6 Hz, CHN), 3.55 (d, 1H, J=13.5 Hz, CHHSO$_2$), 3.48 (d, 2H, J=13.5 Hz, CHHSO$_2$), 2.10-2.25 (m, 2H, camphor ring protons), 1.75-2.00 (m, 3H, camphor ring protons), 1.35-1.50 (m, 2H, camphor ring protons), 1.20 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); exact mass 345.1402 (345.1399 calcd. for $C_{19}H_{23}NO_3S$); Anal. calcd for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71; N, 4.05; Found: C, 65.88; H, 6.81; N, 4.10.

4-(E)-3'-Methylbutenoyl-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]-decane-5,5-dioxide (124)

The literature procedure[136] for generation of analogous compounds was followed. 3-Methylbut-2-enoic acid (**120**) (1.01 g, 10.1 mmol) was dissolved in thionyl chloride (4.0 mL, 6.5 g, 55 mmol) and after 10 min the excess thionyl chloride was removed *in vacuo*. The 3-methylbut-2-enoyl chloride (**119**) was used below without further purification.

The literature procedure[135] for generation of analogous compounds was adapted using the amounts outlined below. Compound **115** (2.17 g, 10.1 mmol) was dissolved in $PhCH_3$ (50 mL) and added to NaH (0.51 g, 11 mmol) in $PhCH_3$ (25 mL). The acid chloride **119** was added and the mixture was stirred for 45 min. H_2O (30 mL) was added and the layers were separated. The aqueous phase was washed with $CHCl_3$ (3 X 30 mL) and the pooled organic phases were dried with Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (hexanes: EtOAc 4:1) gave a colourless solid (0.30 g, 1.0 mmol, 10 % yield): mp 137.5-138 °C; IR ($CHCl_3$ cast) 2989, 1681, 1637, 1308 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.33 (s, 1H, C-2'H), 3.92 (dd, 1H, J=5.5, 7.7 Hz, CHN), 3.50 (d, 1H, J=13.5 Hz,

$CHHSO_2$), 3.43 (d, 1H, J=13.5 Hz, $CHHSO_2$), 2.16 (s, 3H, C-3'CH_3), 2.05-2.20 (m, 2H, camphor ring protons), 1.96 (s, 3H, C-3'CH_3), 1.85-2.00 (m, 3H, camphor ring protons), 1.30-1.45 (m, 2H, camphor ring protons), 1.18 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); exact mass 297.1400 (297.1399 calcd. for $C_{15}H_{23}NO_3S$); Anal. Calcd for $C_{15}H_{23}NO_3S$: C, 60.58; H, 7.79; N, 4.71. Found: C, 60.38; H, 7.92; N, 4.71.

4-(2'-Methylpropenoyl)-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo-[5.2.1.$0^{3,7}$]decane-5,5-dioxide. (125)

The literature procedure[135] was followed using the amounts outlined below. Compound **115** (2.20 g, 10.2 mmol) was dissolved in $PhCH_3$ (50 mL) and added to sodium hydride (0.56 g, 12 mmol) in $PhCH_3$ (50 mL). Methacryloyl chloride (**121**) (1.20 mL, 1.28 g, 12.2 mmol) was added and the mixture was stirred for 19 h. H_2O (20 mL) was added and the layers were separated. The aqueous phase was washed with $CHCl_3$ (3 X 10 mL) and the pooled organic phases were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes: EtOAc 4:1) gave the known **125** as a colourless solid (2.71 g, 9.56 mmol, 94 % yield): mp 146-147 °C (lit[135] mp 149-150 °C); IR ($CHCl_3$ cast) 2990, 1672, 1330, 1195 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.69 (d, 1H, J=1.0 Hz, CHH vinyl), 5.65 (dd, 1H, J=1.0, 2.8 Hz, CHH vinyl), 4.04 (dd, 1H, J=5.0, 7.0 Hz, CHN), 3.52 (d, 1H, J=13.8 Hz, $CHHSO_2$), 3.39 (d, 1H, J=13.8 Hz, $CHHSO_2$), 1.85-2.10 (m, 8H, camphor ring protons & CH_3 methacryloyl), 1.23 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); exact mass 283.1241 (283.1242 calcd. for $C_{14}H_{21}NO_3S$); Anal. Calcd. for C, 59.34; H, 7.47; N, 4.94; Found: C, 59.36; H, 7.17; N, 4.87.

(2*S*,3*R*)-4-[2-(*N*-Phthalimido-3-methylaziridinyl)carbonyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (127) and (2*R*,3*S*)-4-[2-(*N*-Phthalimido-3-methylaziridinyl)carbonyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo-[5.2.1.$0^{3,7}$]decane-5,5-dioxide (126)

The literature procedure[61] for generation of analogous compounds was adapted. To a solution of **122** (156 mg, 0.551 mmol) in dichloromethane (5 mL) was added *N*-aminophthalimide (**84**) (153. mg, 0.945 mmol) under Ar. To the resulting suspension was sprinkled in $Pb(OAc)_4$ of 95 % purity (0.41 g, 0.88 mmol) in portions over 7 min. The mixture was stirred for 15 min, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 2:1) and recrystallization from EtOAc/hexanes gave crystals (0.15 g, 0.34 mmol, 61 % yield) as an unseparated 2:1 mixture of diastereomers (33 % de according to the ^1H NMR): mp 170-171 °C; IR (CH_2Cl_2 cast) 2960, 1760, 1719, 1687, 1330 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ (Major isomer **127**): 7.60-7.85 (m, 4H, PhtH), 3.84 (br. m, 1H, J=4.5, 6.0 Hz, CHN), 3.67 (br. d, 1H, J=4.5 Hz, C-2'H), 3.60 (d, 1H, J=13.5 Hz, CHHSO$_2$), 3.48 (d, 1H, J=13.5 Hz, CHHSO$_2$), 3.44 (dq, 1H, J=5.5, 5.5 Hz, C-3'H), 1.80-2.00 (m, 6H, camphor ring protons), 1.76 (dd, 1H, J=7.5, 13.5 Hz, CHHCHN), 1.55 (d, 3H, J=5.5 Hz, C-4'H_3), 1.38 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); (minor isomer **126**): 7.60-7.85 (m, 4H, PhtH), 3.95 (dd, 1H, J=5.0, 8.0 Hz, CHN), 3.87 (d, 1H, J= 5.5 Hz, C-2'H), 3.57 (d, 1H, J=13.5 Hz, CHHSO$_2$), 3.48 (dd, 1H, J=13.5 Hz, CHHSO$_2$), 2.99 (dq, 1H, J=5.5, 5.5 Hz, C-3'H), 2.27 (ddd, 1H, J=3.5, 8.0, 14.0 Hz, CHHCHN), 2.13 (dd, 1H, J=8.0, 14.0 Hz, CHHCHN), 1.80-2.00 (m, 5H, camphor ring protons), 1.49 (d, 3H, J=6.0 Hz, C-4'H_3), 1.38 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 164.70 (C=O), 164.62 (C=O), 134.15 (ArC), 133.62 (ArC), 130.43 (ArC), 128.21 (ArC), 123.25 (ArC), 122.68 (ArC), (aliphatic carbons): 65.30, 65.18, 53.22, 53.06, 49.17, 48.76, 47.98, 47.89, 45.90, 45.10, 44.75, 44.68, 38.21, 37.42, 32.89, 32.79, 26.52, 20.86, 20.73, 20.00, 16.39;

exact mass 443.1509 (443.1515 calcd. for $C_{22}H_{25}N_3O_5S$); Anal. Calcd for $C_{22}H_{25}N_3O_5S$: C, 59.58; H, 5.68; N, 9.47. Found: C, 59.59; H, 5.71; N, 9.22.

(2*R*,3*S*)-4-[2-(*N*-Phthalimido-3-phenylaziridinyl)carbonyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decane-5,5-dioxide (129) and (2*S*,3*R*)-4-[2-(*N*-Phthalimido-3-phenylaziridinyl)carbonyl-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decane-5,5-dioxide (128)

The literature procedure[61] for generation of analogous compounds was adapted. To a solution of **123** (201 mg, 0.567 mmol) in dichloromethane (5 mL) was added *N*-aminophthalimide (**84**) (140. mg, 0.862 mmol) under Ar. To the resulting suspension was sprinkled in Pb(OAc)$_4$ of 95 % purity (0.40 g, 0.86 mmol) in portions over 7 min. The mixture was stirred for 15 min, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 2:1) gave a solid (0.26 g, 0.52 mmol, 90 % yield) as an unseparated 9:1 mixture of diastereomers (80 % de according to ^{1}H NMR): mp 198-200 °C; IR (CHCl$_3$ cast) 2960, 1770, 1720, 1680, 1330 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$) δ (Major isomer **129**): 7.60-7.80 (m, 4H, PhtH), 7.50-7.60 (m, 2H, PhH), 7.30-7.45 (m, 3H, PhH), 4.47 (d, 1H, J=5.0 Hz, C-3'H), 4.18 (d, 1H, J=5.0 Hz, C-2'H), 3.90 (dd, 1H, J=4.6, 7.2 Hz, CHN), 3.62 (d, 1H, J=13.6 Hz, CHHSO$_2$), 3.48 (d, 1H, J=13.6 Hz, CHHSO$_2$), 1.65-2.10 (m, 5H, camphor ring protons), 1.20-1.50 (m, 2H, camphor ring protons), 1.40 (s, 3H, CH$_3$), 1.00 (s, 3H, CH$_3$); (minor isomer **128**): 7.60-7.80 (m, 4H, PhtH), 7.50-7.60 (m, 2H, PhH), 7.30-7.45 (m, 3H, PhH), 5.28 (d, 1H, J=5.0 Hz, C-3'H), 4.07 (d, 1H, J=5.0 Hz, C-2'H), 3.99 (dd, 1H, J=5.0, 5.8 Hz, CHN), 3.62 (d, 1H, J=13.6 Hz, CHHSO$_2$), 3.48 (d, 1H, J=13.6 Hz, CHHSO$_2$), 1.65-2.10 (m, 5H, camphor ring protons), 1.20-1.50 (m, 2H, camphor ring protons), 1.40 (s, 3H, CH$_3$), 1.00 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz, CDCl$_3$) 164.51 (C=O), 164.08 (C=O), 134.28 (ArC), 133.93 (ArC), 130.38 (ArC), 128.59 (ArC), 128.16 (ArC), 127.61 (ArC), 122.97 (ArC), 65.31 (CHPh), 53.19 (CHCO), 50.82 (CHN), 48.65 (CH$_2$SO$_2$), (Aliphatic carbons): 47.90, 45.23, 44.78, 37.46, 32.89, 26.50, 20.76, 19.99; exact mass 505.1666 (505.1671 calcd. for $C_{27}H_{27}N_3O_5S$); Anal. Calcd for $C_{27}H_{27}N_3O_5S$: C, 64.14; H, 5.38; N, 8.31. Found: C, 64.17; H, 5.40; N, 8.27.

4-[2-(*N*-Phthalimido-3,3-dimethylaziridinyl)carbonyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (130)

The literature procedure[61] for generation of analogous compounds was adapted. To a solution of **124** (99.0 mg, 0.333 mmol) in dichloromethane (2.5 mL) was added *N*-aminophthalimide (**84**) (109. mg, 0.671 mmol) under Ar. To the resulting suspension was sprinkled in $Pb(OAc)_4$ of 95 % purity (0.25 g, 0.58 mmol) in portions over 2 min. The mixture was stirred for 40 min, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 4:1 then $CHCl_3$ then $CHCl_3$:CH_3OH 9:1) gave a colourless solid (102 mg, 0.223 mmol, 67 % yield) (≥ 95 % de according to ^1H NMR): mp 196-196.5 °C (dec); IR ($CHCl_3$ cast) 2962, 1775, 1719, 1391 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.65-7.90 (m, 4H, Pht$\underline{H}$), 3.96 (dd, 1H, J=5.0, 7.8 Hz, C$\underline{H}$N), 3.89 (s, 1H, C-2'$\underline{H}$), 3.56 (d, 1H, J=13.8 Hz, C$\underline{H}$HSO_2), 3.46 (d, 1H, J=14.0 Hz, CH$\underline{H}SO_2$), 1.80-2.40 (m, 6H, camphor ring protons), 1.35-1.55 (m, 1H, camphor ring protons), 1.48 (s, 3H, C-3'C$\underline{H}_3$), 1.45 (s, 3H, C-3'C$\underline{H}_3$), 1.29 (s, 3H, C$\underline{H}_3$), 1.01 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.28 ($\underline{C}$=O), 165.12 ($\underline{C}$=O), 134.72 (Ar$\underline{C}$), 134.10 (Ar$\underline{C}$), 130.63 (Ar$\underline{C}$), 124.02 (Ar$\underline{C}$), 123.14 (Ar$\underline{C}$), 65.03 ($\underline{C}$(α)), 53.06 ($\underline{C}H_2SO_2$), 52.06 ($\underline{C}_q$), 51.64 (CHN), 49.16 ($\underline{C}_q$), 48.00 ($\underline{C}_q$), 44.64 ($\underline{C}$H bridgehead), 38.22 ($\underline{C}H_2$), 32.70 ($\underline{C}H_2$), 26.55 ($\underline{C}H_2$), 20.84 ($\underline{C}H_3$), 19.93 ($\underline{C}H_3$), 19.72 ($\underline{C}H_3$), 18.88 ($\underline{C}H_3$); exact mass 457.1675 (457.1671 calcd. for $C_{23}H_{27}N_3O_5S$); Anal. Calcd. for $C_{23}H_{27}N_3O_5S$: C, 60.38; H, 5.95; N, 9.18. Found: C, 60.33; H, 5.73; N, 9.52.

(2*R*)-4-[2-(*N*-Phthalimido-2-methylaziridinyl)carbonyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (131) and (2*S*)-4-[2-(*N*-Phthalimido-2-methylaziridinyl)carbonyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (132)

The literature procedure[61] for generation of analogous compounds was adapted. To a solution of **125** (444 mg, 1.57 mmol) in dichloromethane (2.25 mL) was added *N*-aminophthalimide (**84**) (40.9 mg, 0.252 mmol) under Ar. To the resulting suspension was added dropwise $Pb(OAc)_4$ of 95 % purity (163 mg, 0.349 mmol) in dichloromethane (2.25 mL) over 15 min. The mixture was stirred for 15 min, filtered and separated on an MPLC column (Merck PF_{254} SiO_2, hexanes:EtOAc 1:1) to give a colourless solid (13.7 mg, 30.9 μmol, 12 % yield) as an unseparated 5.7:1 mixture of diastereomers (70 % de according to ^1H NMR): mp 218-219 °C; IR ($CHCl_3$ cast) 2960, 1780, 1772, 1725, 1700, 1337 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (Major isomer **132**): 7.65-7.75 (m, 4H, Ar$\underline{H}$), 3.93 (dd, 1H, J=6.0, 6.0 Hz, $C\underline{H}N$), 3.48 (d, 1H, J=13.8 Hz, $C\underline{H}HSO_2$), 3.44 (d, 1H, J=13.8 Hz, $CH\underline{H}SO_2$), 3.32 (d, 1H, J=3.0 Hz, C-3'$\underline{H}$H), 3.16 (d, 1H, J=3.0 Hz, C-3'H$\underline{H}$), 2.16 (d, 2H, J=6.0 Hz, $C\underline{H_2}CHN$), 1.85-2.00 (m, 2H, camphor ring protons), 1.74 (s, 3H, $C\underline{H_3}$), 1.30-1.50 (m, 3H, camphor ring protons), 1.18 (s, 3H, $C\underline{H_3}$), 0.98 (s, 3H, $C\underline{H_3}$); (minor isomer **131**): 3.83 (m, 1H, $C\underline{H}N$), 1.15 (s, 3H, $C\underline{H_3}$), 0.96 (s, 3H, $C\underline{H_3}$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.65 ($\underline{C}$=O), 134.12 (Ar$\underline{C}$), 123.16 (Ar$\underline{C}$), (Aliphatic carbons): 65.09, 52.93, 47.96, 44.26, 42.20, 38.04, 32.49, 26.52, 20.36, 19.85, 16.06; exact mass 443.1514 (443.1515 calcd. for $C_{22}H_{25}N_3O_5S$).

Ethyl (E)-2-Methyl-3-[(3,4-methylenedioxy)phenyl]propenoate (136)

The literature procedure[137] was modified. (Carbethoxyethylidene)triphenylphosphorane (**135**) of 98 % purity (purchased from Sigma Chemical Co.) (2.58 g, 6.98 mmol) and **134** (1.05 g, 6.98 mmol) were heated to reflux in $PhCH_3$ (50 mL) for 5h. A yellow precipitate was filtered from the solution and the solution was concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 8:1) gave the known **136** as a colourless oil (1.62 g, 6.91 mmol, 99 % yield): IR ($CHCl_3$ cast) 2961, 2902, 1704, 1491 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.60 (s, 1H, C$\underline{H}$ vinyl), 6.80-7.00 (m, 3H, Ar$\underline{H}$), 5.99 (s, 2H, $C\underline{H}_2O_2$), 4.26 (q, 2H, J=7.0 Hz, $C\underline{H}_2CH_3$), 2.12 (d, 3H, J=1.5 Hz, $C\underline{H}_3C{=}CH$), 1.35 (t, 3H, J=7.0 Hz, $C\underline{H}_3CH_2$); exact mass 234.0891 (234.0892 calcd. for $C_{13}H_{14}O_4$; Anal. Calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02; Found: C, 66.43; H, 6.32.

(E)-2-Methyl-3-(3',4'-methylenedioxy)phenylpropenoic Acid (137)

The literature procedure[138] was modified. A solution of **136** (1.23 g, 5.79 mmol) in THF (10 mL) with NaOH (6.0 mL, 1.0 M, 5.8 mmol) and Me_4NOH (0.01 g, 60 mmol) was stirred for 4 days at 20 °C. HCl (6 mL, 1 M) was added and the resulting precipitate was filtered to give the known **137** as a colourless solid (914 mg, 4.44 mmol, 84 % yield): mp 201-201.5 °C (lit[138] mp 200-201 °C); IR ($CHCl_3$ cast) 3410, 2924, 1663, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H, C$\underline{H}$ vinyl), 6.80-7.00 (m, 3H, Ar$\underline{H}$), 6.01 (s, 2H, $C\underline{H}_2O_2$), 2.12 (s, 3H, $C\underline{H}_3$); exact mass 206.0574 (206.0579 calcd. for $C_{11}H_{10}O_4$); Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.08; H, 4.89; Found: C, 63.62; H, 4.91.

4-(E)-2-[Methyl-3-[(3,4-methylenedioxy)phenyl]propenoyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (139)

The literature procedure[136] for generation of analogous compounds was adapted. A solution of **137** (754. mg, 3.65 mmol) was heated to reflux in thionyl chloride (1.56 mL, 2.56 g, 21.5 mmol) for 30 min and the excess thionyl chloride was removed *in vacuo* to give a colourless oil: IR ($CHCl_3$ cast) 1750 cm^{-1}. The 2-methyl-3-(3',4'-methylenedioxy)phenylpropenoyl chloride (**138**) was used below without further purification.

The literature procedure[135] for generation of analogous compounds was followed using the amounts outlined below. Compound **115** (0.84 g, 3.9 mmol) was dissolved in $PhCH_3$ (15 mL) and added to sodium hydride (0.19 g, 4.0 mmol) in $PhCH_3$ (7.5 mL). Compound **138** (820. mg, 3.65 mmol) in $PhCH_3$ (15 mL) was added and the mixture was stirred for 160 min. H_2O (10 mL) was added and the layers were separated. The aqueous phase was washed with $CHCl_3$ (3 X 10 mL) and the pooled organic phases were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 7:3) gave a colourless solid (0.89 g, 2.24 mmol, 60 % yield): mp 160-160.5 °C; IR ($CHCl_3$ cast) 2960, 1674, 1489, 1237 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10-6.78 (m, 4H, $Ar\underline{H}$ & $C\underline{H}$ vinyl), 5.96 (s, 2H, $C\underline{H}_2O_2$), 4.08 (dd, 1H, J=4.8, 7.2 Hz, $C\underline{H}N$), 3.50 (d, 1H, J=13.5 Hz, $C\underline{H}HSO_2$), 3.40 (d, 1H, J=13.5 Hz, $CH\underline{H}SO_2$), 2.11 (s, 3H, $C\underline{H}_3C{=}C$), 1.75-2.10 (m, 5H, camphor ring protons), 1.30-1.50 (m, 5H, camphor ring protons), 1.27 (s, 3H, $C\underline{H}_3$), 0.99 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 ($\underline{C}{=}O$), 147.5 ($Ar\underline{C}$), 138.7 ($Ar\underline{C}$), 129.9 ($Ar\underline{C}$), 129.2 ($Ar\underline{C}$), 124.2 ($Ar\underline{C}$), 109.4 ($Ar\underline{C}$), 108.2 ($\underline{C}{=}CC{=}O$), 101.1 ($\underline{C}C{=}O$), (Aliphatic carbons): 65.3, 53.4, 47.8, 47.6, 45.1, 38.1, 33.0, 26.4, 21.2, 19.7, 14.7; exact mass 403.1459 (403.1453 calcd. for $C_{21}H_{25}NO_5S$); Anal. Calcd. for $C_{21}H_{25}NO_5S$: C, 62.51; H, 6.24; N, 3.47; Found: C, 62.27; H, 6.13; N, 3.42.

4-[3-((4-Methoxyphenyl)methylthio)-2-((*N*-phthalimido)amino)propanoyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decane-5,5-dioxide[81] (140)

To a solution of **116** (0.36 g, 0.84 mmol) in dichloromethane (5 mL) was added *p*-methoxybenzylthiol (**95**) (1.00 mL, 1.29 g, 8.38 mmol) followed by boron trifluoride etherate (0.74 mL, 0.83 g, 5.9 mmol). After 25 min the solution was concentrated *in vacuo*. Flash chromatography twice (hexanes:EtOAc 3:2) and recrystallization of the resulting residue from EtOAc gave a colourless powder (272 mg, 0.466 mmol, 56 % yield): mp 203-205

°C; IR ($CHCl_3$ cast) 3280, 2959, 1785, 1727, 1695, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60-7.80 (m, 4H, Pht$\underline{H}$), 7.27 (d, 2H, J=12.0 Hz, Ar$\underline{H}$), 6.78 (d, 2H, J=12.0 Hz, Ar$\underline{H}$), 4.51 (t, 1H, J=6.9 Hz, C-2'$\underline{H}$), 3.84 (d, 1H, J=13.0 Hz, $C\underline{H}HSO_2$), overlapping with 3.80 (m, 1H, C$\underline{H}$N sultam), 3.76 (d, 1H, J=13.0 Hz, $CH\underline{H}SO_2$), 3.70 (s, 3H, $C\underline{H}_3$), 3.33 (d, 1H, J=13.8 Hz, C$\underline{H}$HAr), 3.26 (d, 1H, J=13.8 Hz, CH$\underline{H}$Ar), 2.80 (d, 2H, J=6.9 Hz, C-3'$\underline{H}_2$), 2.21 (m, 1H, C$\underline{H}$HCHN sultam), 2.00 (dd, 1H, J=8.5, 17.0 Hz, CH$\underline{H}$CHN sultam), 1.70-1.85 (m, 3H, camphor ring $\underline{H}$), 1.15-1.35 (m, 2H, camphor ring $\underline{H}$), 0.78 (s, 3H, $C\underline{H}_3$), 0.70 (s, 3H, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.12 ($\underline{C}$=NS), 166.09 ($\underline{C}$=ONC), 158.54 (Ar$\underline{C}$), 134.01 (Ar$\underline{C}$), 130.28 (Ar$\underline{C}$), 130.13 (Ar$\underline{C}$), 129.32 (Ar$\underline{C}$), 123.19 (Ar$\underline{C}$), 113.77 (Ar$\underline{C}$), 65.55 ($\underline{C}\alpha$), 59.94 ($\underline{C}$HNS), 55.10 ($\underline{C}SO_2$), 52.90 ($O\underline{C}H_3$), 48.28, 47.45, 44.55, 37.61, 34.81, 32.91, 30.72, 26.27, 20.39 ($\underline{C}H_2Ar$), 19.69 ($CH\underline{C}H_2S$); exact mass 583.1807 (583.1811 calcd. for $C_{29}H_{33}N_3O_6S_2$); Anal. Calcd. for $C_{29}H_{33}N_3O_6S_2$: C, 59.67; H, 5.70; N, 7.20. Found: C, 59.31; H, 5.83; N, 7.05.

4-[(3-Phenyl)methylthio)-2-((*N*-phthalimido)amino)propanoyl]-(7*S*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0^{3,7}]decane-5,5-dioxide (141)

The literature procedure[81] for generation of analogous compounds was adapted. To a solution of **116** (54.3 mg, 0.126 mmol) in benzylthiol (**27**) (1.0 mL, 1.1 g, 8.5 mmol) at 20 °C was added boron trifluoride etherate (0.86 g, 6.0 mmol). After 95 min, flash chromatography (hexanes:EtOAc 3:2) in the hood and trituration of the resulting oil with Et_2O gave a colourless solid (56.2 mg, 0.982 mmol, 78 % yield): mp 93-95 °C; IR ($CHCl_3$ cast) 3280, 2960, 1780, 1728, 1690, 1382 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.70-7.85 (m, 4H, Pht$\underline{H}$), 7.25-7.45 (m, 5H, Ph$\underline{H}$), 5.59 (br. s, 1H, N$\underline{H}$), 4.60 (dd, 1H, J=7.2, 7.2 Hz, C$\underline{H}$(α)), 3.94 (m, 3H, $S C\underline{H}_2Ph$ & C$\underline{H}$N), 3.42 (d, 1H, J=13.8 Hz, $C\underline{H}H_2SO_2$), 3.35 (d, 1H, J=13.8 Hz, $CH\underline{H}_2SO_2$), 2.90 (d, 2H, J=7.7 Hz, $CH_2(\beta)$), 2.31 (m, 1H, C$\underline{H}$HCHN), 2.10 (dd, 1H, J=7.0, 12.0 Hz, CH$\underline{H}$CHN), 1.85-1.95 (m, 3H, camphor ring protons), 1.25-1.40 (m, 2H, camphor ring protons), 0.86 (s, 3H, C$\underline{H}_3$), 0.81 (s, 3H, C$\underline{H}_3$); exact mass 553.1707 (553.1705 calcd. for $C_{28}H_{31}N_3O_5S_2$); Anal. Calcd for $C_{28}H_{33}N_3O_5S_2$: C, 58.83; H, 5.82; N, 7.35. Found: C, 59.19; H, 5.41; N, 7.42.

***iso*-Propyl (*S*)-*N*-Phthalimidoaziridine-2-carboxylate (143)**

The literature procedure[93, 139] for generation of analogous compounds was adapted. A stirred solution of **116** (85.8 mg, 0.200 mol) in THF (1 mL), $PhCH_3$ (0.5 mL), and titanium isopropoxide (0.20 mL, 280 mg, 1.0 mmol) was heated to 70 °C for 88 h. HCl (1M, 2 mL) was added and the mixture was extracted with Et_2O (3 X 5 mL). The pooled Et_2O phases were washed with $NaHCO_3$ (10 %, 5 mL), and the basic phase was washed with Et_2O (2 X 5 mL). The pooled Et_2O phases were dried with Na_2SO_4, filtered, and concentrated *in vacuo* to give an oil. HPLC purification [C8 bondapak, 10 % CH_3CN/H_2O (5 min isocratic) gradient over 30 min to 100 % CH_3CN (5 min isocratic), flow=1 mL/min, UV=254 nm minus 314 nm, t_R=24.8 min; reinjection on the same column, 55 % CH_3CN isocratic, flow=1 mL/min, t_R=5.72 min] gave a colourless oil (1.7 mg, 6.2 μmol, 3 % yield). IR ($CHCl_3$ cast) 3280, 2940, 1721, 1376 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.65-7.85 (m, 4H, Pht$\underline{H}$), 5.16 & 4.93 (2 X m, 1H, 2 X J=7.0 Hz, C$\underline{H}(CH_3)_3$), 3.12 (dd, 1H, J=5.5, 7.8 Hz, C$\underline{H}$CHH), 2.85 (dd, 1H, J=1.8, 5.5 Hz, C$\underline{H}$H), 2.81 (dd, 1H, J=1.8, 7.8 Hz, CH$\underline{H}$), 1.36 & 1.23 (2 X d, 3H, 2 X J=7.0 Hz, C$\underline{H}_3$), 1.30 & 1.20 (2 X d, 3H, 2 X J=7.0 Hz, C$\underline{H}_3$); A 5 mol % solution of $Eu(HFC)_3$ in $CDCl_3$: δ 1.70 (d, 2.1H, J=7.0 Hz, C$\underline{H}_3$ first conformer), 1.48 (d, 2.0H, J=7.0 Hz, C$\underline{H}_3$ first conformer), 1.26 (t, 1.8H, J=6.0 Hz, $(C\underline{H}_3)_2$ second conformer); exact mass 274.0954 (274.0954 calcd. for $C_{14}H_{14}N_2O_4$).

iso-Propyl (*R*)-*N*-Phthalimidoaziridine-2-carboxylate (144)

The literature procedure[93, 139] for generation of analogous compounds was adapted. A stirred solution of **147** (107 mg, 0.249 mmol) in THF (2 mL) and titanium isopropoxide (0.37 mL, 0.35 g, 1.2 mmol) was heated to reflux for 25 min. HCl (1M, 2 mL) was added and the mixture was washed with Et_2O (3 X 5 mL). The pooled organic phases were washed with $NaHCO_3$ (5 mL, 10 %), dried with Na_2SO_4, and concentrated *in vacuo* to give an oil (78.7 mg). HPLC purification [C8 bondapak, 10 % CH_3CN/H_2O (5 min isocratic) gradient over 30 min to 100 % CH_3CN (5 min isocratic), flow=1 mL/min, UV=254 nm minus 314 nm, t_R=24.8 min; reinjection on the same column, 55 % CH_3CN isocratic, flow=1 mL/min, t_R=5.72 min] gave a colourless oil (4.8 mg, 18 μmol, 7 % yield, 27 % overall yield). IR ($CHCl_3$ cast) 3290, 2980, 1770, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 7.65-7.85 (m, 4H, Pht$\underline{H}$), 5.16 & 4.93 (2 x m, 1H, 2 x J=7.0 Hz, $C\underline{H}(CH_3)_3$), 3.12 (dd, 1H, J=5.5, 7.8 Hz, $C\underline{H}CHH$), 2.85 (dd, 1H, J=1.8, 5.5 Hz, $C\underline{H}H$), 2.81 (dd, 1H, J=1.8, 7.8 Hz, $CH\underline{H}$), 1.36 & 1.23 (2 x d, 3H, 2 x J=7.0 Hz, $C\underline{H}_3$), 1.30 & 1.20 (2 x d, 3H, 2 x J=7.0 Hz, $C\underline{H}_3$); exact mass 274.0952 (274.0954 calcd. for $C_{14}H_{14}N_2O_4$).

^1H NMR Study of 143 and 144 Using Chiral Shift Reagent.

A solution of **144** (0.1 mg, 0.4 μmol) and **143** (0.2 mg, 0.7 μmol) in $CDCl_3$ and $Eu(HFC)_3$ (4 drops, 0.13 μmol/drop, 0.52 μmol, 48 mol %) at 20 °C showed the following spectral characteristics: ^1H NMR (200 MHz, $CDCl_3$) δ 1.22-1.31 (m, 4.0H, $(C\underline{H}_3)_2$ of the minor conformations of both enantiomeric starting materials), 1.42 (d, 1.5H, J=6.2 Hz, $C\underline{H}_3$ of **144**), 1.54 (d, 2.7H, J=6.2 Hz, $C\underline{H}_3$ of **143**), 1.84 (m, 3.9H, $C\underline{H}_3$ of **144** & $C\underline{H}_3$ of **143**).

4-Propenoyl-(7*R*)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (146)

The literature procedure[135] for generation of analogous compounds was followed using the amounts outlined below. L-2,10-Camphorsultam (**145**) (3.0 mg, 14 mmol), was dissolved in $PhCH_3$ (40 mL) and added to sodium hydride (1.14 g, 23.8 mmol) in $PhCH_3$ (10 mL). Acryloyl chloride (2.5 mL, 2.8 mg, 28. mmol) was added and the mixture stirred for 1 h. H_2O (20 mL) was added and the layers were separated. The aqueous phase was washed with EtOAc (3 X 50 mL), and the pooled organic phases were dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 4:1) gave a colourless solid (0.70 g, 2.5 mmol, 18 % yield): mp 196-197 °C (lit[135] mp 196-197 °C); IR ($CHCl_3$ cast) 2960, 1675, 1610, 1310 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.88 (dd, 1H, J=10.8, 16.2 Hz, $C\underline{H}$ vinyl), 6.41 (dd, 1H, J=2.0, 16.2 Hz, $C\underline{H}$ vinyl), 5.87 (dd, 1H, J=2.0, 10.8 Hz, $C\underline{H}$ vinyl), 3.95 (dd, 1H, J=5.4, 7.2 Hz, $C\underline{H}N$), 3.53 (d, 1H, J=13.8 Hz, $C\underline{H}HSO_2$), 3.46 (d, 1H, J=13.8 Hz, $CH\underline{H}SO_2$), 1.85-2.20 (m, 5H, camphor ring protons), 1.30-1.45 (m, 2H, $C\underline{H_2}CHN$), 1.17 (s, 3H, $C\underline{H_3}$), 0.97 (s, 3H, $C\underline{H_3}$); exact mass 269.1084 (269.1086 calcd. for $C_{13}H_{19}NO_3S$).

(2*S*)-4-[2-(*N*-Phthalimidoaziridinyl)carbonyl]-(7*R*)-10,10-dimethyl-5-thia-4-azatri-cyclo[5.2.1.$0^{3,7}$]decane-5,5-dioxide (147)

The literature procedure[61] for generation of analogous compounds was adapted. To a solution of **146** (0.70 g, 2.5 mmol) in dichloromethane (20 mL) was added *N*-amino-phthalimide (**84**) (0.45 g, 2.8 mmol) under Ar. To the resulting suspension was sprinkled in $Pb(OAc)_4$ (1.35 g of 95 % purity, 2.89 mmol) in portions over 18 min. The mixture was stirred for 20 min, filtered and concentrated *in vacuo*. Flash chromatography (hexanes: EtOAc 2:1) gave colourless crystals (0.79 g, 1.8 mmol, 72 % yield) as an 8:1 mixture of diastereomers according to ^1H NMR. Recrystallization from either $CHCl_3/Et_2O$ or $PhCH_3$/hexanes caused the major isomer **147** to precipitate: mp 209-210 °C; IR

($CHCl_3$ cast) 2960, 1722, 1696, 1240 cm^{-1}; ^1H NMR (300MHz, $CDCl_3$) 7.73-7.98 (m, 4H, ArH), 3.95 (dd, 1H, J=4.9, 7.8 Hz, CHN), 3.83 (dd, 1H, J=5.5, 7.8 Hz, C-2'H), 3.63 (d, 1H, J=14.0 Hz, $CHHSO_2$), 3.49 (d, 1H, J=14.0 Hz, $CHHSO_2$), 3.02 (dd, 1H, J=1.6, 7.5 Hz, C-3'HH), 2.91 (dd, 1H, J=1.6, 5.5 Hz, C-3'HH), 2.31 (d, 1H, J=14.0 Hz, C-2HH), 2.13 (dd, 1H, J=7.8, 14.0 Hz, C-2HHCHN), 1.94 (m, 3H, camphor ring protons), 1.34 (m, 5H, CH_3 & camphor ring protons), 1.02 (s, 3H, CH_3); exact mass 429.1367 (429.1358 calcd. for $C_{21}H_{23}N_3O_5S$).

Di-*n*-propyl Benzene-1,2-dicarboxylate (150) and *n*-Propyl *N'*-Phthalimido-aziridine-2-carboxylate (149)

The literature procedure[93] for generation of analogous compounds was adapted. To a suspension of **88** (200. mg, 0.768 mmol) in 1-propanol (3.0 mL, 2.4 mg, 40. mmol) at 80 °C was added titianium isopropoxide (0.1 mL, 90 mg, 0.3 mmol) and the mixture was stirred for 45 min. HCl (1M, 5 mL) was added and the mixture was washed with pentane (2 X 15 mL). The pooled organic phases were washed with $NaHCO_3$ (3 mL, 10 %), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 4:1) gave the known **150** as a colourless oil (0.10 g, 0.36 mmol, 46 % yield): lit[140] mp 304-305 °C; IR ($CHCl_3$ cast) 2969, 1723, 1266 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.50-7.80 (m, 4H, ArH), 4.27 (t, 4H, J=6.5 Hz, 2 X CH_2O), 1.76 (tq, 4H, J=6.5 Hz, 2 X CH_2CH_3), 1.00 (t, 6H, J=6.5 Hz, 2 X CH_3); exact mass 250.1200 (250.1205 calcd. for $C_{14}H_{18}O_4$).

The second compound isolated from the column was subjected to flash chromatography (hexanes:EtOAc 2:1) and gave **149** as colourless crystals (0.06 g, 0.2 mmol, 28 % yield): mp 90-92 °C; IR ($CHCl_3$ cast) 2960, 1723, 1377, 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65-7.90 (m, 4H, ArH), 4.26 (ddd, 1H, J=6.6, 6.6, 10.5 Hz, CHHO), 4.18 (ddd, 1H, J=6.6, 6.6, 10.5 Hz, CHHO), 3.19 (dd, 1H, J=5.5, 7.7 Hz, $CHCH_2$), 2.87 (dd, 1H, J=1.9, 5.5 Hz, CHHCH), 2.84 (dd, 1H, J=1.9, 7.7 Hz, CHHCH), 1.75 (tq, 2H, J=7.4, 7.4 Hz, CH$_2$CH$_3$), 1.00 (t, 3H, J=7.4 Hz, CH$_3$); exact mass 274.0953 (274.0954 calcd. for $C_{14}H_{14}N_2O_4$).

(*S*)-Hydrazinoserine (151)

The literature procedure[141] for generation of analogous compounds was adapted. To a solution of **194** (40. mg, 0.11 mmol) in CH_3OH (2 mL) and 3 % $Pd(OH)_2$ on carbon (30 mg, 6 µmol) was added. Hydrogen was introduced and after 10 min the reaction was filtered through Celite. Separation on an MPLC column (RP-8 Merck Lobar, 100 % H_2O, UV=218 nm) gave a colourless oil (0.4 mg, 60 µmol, 60 % yield). AG11 ion retardation resin chromatography (eluted with H_2O) gave a colourless powder: mp >340 °C; IR (CH_3OH cast) 3223, 2990, 1728, 1615, 1414 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.00 (dd, 1H, J=3.6, 12.0 Hz, CHH), 3.97 (dd, 1H, J=4.8, 12.0 Hz, CHH), 3.86 (dd, 1H, J=3.6, 4.8 Hz, CH); ^{13}C NMR (125 MHz, D_2O) δ 174.08 (CO), 67.60 (CH$_2$), 64.76 (CH); FAB MS (glycerol) 121 (MH$^+$).

1-Methoxycarbonyl-3-phenyloxaziridine (155) and Methoxycarbonylbenzamide (163)

The literature procedure[54] was followed using the amounts outlined below. Compound **162** (19.7 g, 120. mmol), $CHCl_3$ (250 mL), K_2CO_3 (141 g, 1.02 mmol) in H_2O (590 mL), and Oxone® (178 g, 109. mmol) in H_2O (1 L) were stirred at 0 °C for 45 min. The organic layer was washed successively with $KHSO_4$ (100 mL, 5 %), $NaHCO_3$ (100 mL, 5 %), and H_2O (100 mL), and then concentrated *in vacuo*. Flash chromatography (pentane:Et_2O:CH_2Cl_2 3:1:1 then Et_2O:CH_2Cl_2 1:1) gave the known **155** as colourless crystals (9.41 g, 52.6 mmol, 43 % yield): mp 40-41 °C (lit[54] mp 41 °C); IR (CH_2Cl_2 cast) 2960, 1774, 1751, 1260 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40-7.50 (m, 5H, ArH), 5.14 & 5.32 (2 X s, 1H, CH), 3.94 & 3.58 (2 X s, 3H, CH$_3$); exact mass 179.0581 (179.0582 calcd. for $C_9H_{10}NO_3$); Anal. Calcd. for $C_9H_{10}NO_3$: C, 60.33; H, 5.06; N, 7.82; Found: C, 60.58; H, 5.05; N, 7.62. The second compound isolated from the column was the known **163** as colourless crystals (1.94 g, 10.8 mmol, 9 % yield): mp 113-114 °C (lit[54] mp 117-118 °C); IR (CH_3OH cast); 3200, 1782, 1511, 1488, 1201 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.45-7.90 (m, 5H, Ar$\underline{H}$), 3.80 (s, 3H, C$\underline{H}_3$); exact mass 180.0659 (180.0660 calcd. for $C_9H_{10}NO_3$); Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82; Found: C, 60.52; H, 5.06; N, 7.86.

N-Trimethylsilylbenzaldimine (161)

The literature procedure[142] was followed using the amounts outlined below. BuLi (7.65 mL, 2.3 M solution in hexanes, 17.6 mmol) was added to freshly distilled HMDS (4.0 mL, 3.1 g, 19 mmol) to give lithium hexamethyldisilazane. The solvent was removed *in vacuo* and the residue was cooled to 0 °C. Then, freshly distilled benzaldehyde (1.85 mL, 1.93 g, 18.2 mmol) was added over 6 min. Distillation with a Vigreux column (10 cm) gave the known **173** as a liquid (0.80 g, 4.5 mmol, 25 % yield): bp 48 °C, 0.7 torr (lit[142] bp 100-102 °C, 19 torr); IR ($CHCl_3$ cast) 3400, 2960, 2800, 1641, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H, C$\underline{H}$N), 7.84 (m, 2H, Ar$\underline{H}$), 7.46 (m, 3H, Ar$\underline{H}$), 0.30 (s, 9H, Si(C$\underline{H}_3$)$_3$); exact mass 194.0970 (197.0974 calcd. for $C_{10}H_{15}NSi$).

N-Methoxycarbonylbenzaldimine (162)

The literature procedure[143] was followed with the modifications outlined below. Compound **161** (0.42 g, 2.4 mmol), $CHCl_3$ (6 mL) and methyl chloroformate (0.19 mL, 0.23 g, 2.5 mmol) were stirred at 0 °C for 10 min, and then stirred at 20 °C for 3 h. The solution was concentrated *in vacuo* and the residue was distilled with a Vigreux column (10 cm) to give the known **162** as a colourless oil (102 mg, 0.622 mmol, 26 %): bp 85 °C, 0.8 torr (lit[143] bp 64 °C, 0.03 torr); IR (CH_2Cl_2 cast) 3318, 2976, 1708, 1526, 1243 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.88 (s, 1H, C$\underline{H}$), 7.35-7.90 (m, 5H, Ar$\underline{H}$), 3.85 (s, 3H, C$\underline{H}_3$); exact mass 163.0633 (163.0633 calcd. for $C_9H_9NO_2$).

Ethyl (*RS*)-1-(Methoxycarbonylamino)-1-phenylmethyl Ether (164)

The literature procedure[54] was followed using the amounts outlined below. Compound **162** (1.50 g, 9.19 mmol), $CHCl_3$ (42 mL, distilled from phosphorous pentoxide), K_2CO_3 (10.7 g, 77.4 mmol) in H_2O (83 mL) and Oxone® (13.6 g, 22.1 mmol) in H_2O (145 mL) were stirred at 0 °C for 45 min. The organic layer was washed successively with $KHSO_4$ (50 mL, 5 %), and $NaHCO_3$ (50 mL, 5 %) and then concentrated *in vacuo*. Normal silica gel chromatography repeated twice (Pentane:Et_2O:CH_2Cl_2 3:1:1) gave **164** as colourless crystals (0.90 g, 4.3 mmol, 47 % yield): mp 66-67 °C; IR (CH_2Cl_2 cast) 3308, 2964, 1698, 1536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, 1H, J=9.0 Hz, $N\underline{H}$), 7.25-7.40 (m, 5H, $Ar\underline{H}$), 5.83 (d, 1H, J=9.0 Hz, $C\underline{H}$), 3.55-3.65 (m, 1H, $C\underline{H}HCH_3$), 3.59 (s, 3H, CH_3), 3.45 (dq, 1H, J=7.0, 16.2 Hz, $CH\underline{H}CH_3$), 1.14 (t, 3H, J=7.0 Hz, $C\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.58 ($\underline{C}O_2$), 128.04 ($Ar\underline{C}$), 127.85 ($Ar\underline{C}$), 126.20 ($Ar\underline{C}$), 82.15 ($\underline{C}H$), 62.20 ($\underline{C}H_3O$), 51.49 ($\underline{C}H_2$), 14.97 ($\underline{C}H_3CH_2$); exact mass 180.0661 (180.0661 calcd. for $C_9H_{10}NO_3$); MS (CI, NH_3) 227 (MNH_4^+); Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69; Found: C, 63.30; H, 7.36; N, 6.66.

(2*S*)-2-[Benzyl(amino)]-3-hydroxypropanoic Acid (166)

The literature procedure[103, 144] was followed using the amounts outlined below. (*S*)-Serine (**165**) (21.2 g, 202 mmol), NaOH (8.04 g, 200. mmol, 2 M), benzaldehyde (40.0 mL, 41.8 g, 394 mmol), and $NaBH_4$ (4.56 g, 120. mmol) were stirred for a total of 3 h. The mixture was washed with Et_2O (3 X 75 mL) and the aqueous phase was acidified with HCl (2 M) to bring the pH ≤ 6.2. The mixture was filtered and the residue was recrystallized from H_2O to give the known **166** as colourless needles (11.6 g, 59.2 mmol, 29 % yield): mp 230-231 °C (lit mp 220-222,[103] 240 °C[144]); IR (KBr disk) 3280, 3000, 2640, 1642, 1593, 1554, 1067 cm^{-1}; ^1H NMR (200 MHz, D_2O/DO_2CCD_3) δ 7.45-7.55 (m, 5H, $Ar\underline{H}$), 4.32 (s, 2H, $C\underline{H}_2Ph$), 4.02 (d, 2H, J=4.0 Hz, $C\underline{H}_2OH$), 3.85 (t, 1H, J=4.0 Hz, CHN); exact mass 164.0710 (164.0711 calcd. for $C_9H_{10}NO_2$); MS (CI, NH_3) 196 (MH^+); Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17; Found: C, 61.41; H, 6.72; N, 7.14.

(2*S*)-2-[Benzyl(amino)]-3-hydroxypropanoic Acid Benzyltrimethylammonium Salt (167)

The literature procedure[145] for generation of analogous compounds was adapted. To a solution of **166** (1.75 g, 8.96 mmol) in H_2O (25 mL) was added benzyltrimethylammonium hydroxide of 40 % purity (4.05 mL, 1.50 g, 8.96 mmol) and the solvent removed *in vacuo* to give an oil (3.31 g, 8.90 mmol, 99 % yield): IR (CH_2Cl_2 cast) 3280, 3020, 1595, 1460 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.10-7.60 (m, 10H, ArH), 4.43 (s, 2H, N^+CH_2), 3.71 (m, 1H, CH), 3.65 (m, 2H, CH_2CH), 3.33 (s, 2H, NCH_2), 3.02 (s, 9H, $(CH_3)_3$); exact mass 150.0921 (150.0919 calcd. for $C_9H_{12}NO$); Anal. Calcd. for $C_{20}H_{28}N_2O_3 \cdot (H_2O)_{1.5}$: C, 64.67; H, 8.41; N, 7.54; Found: C, 64.55; H, 8.09; N, 7.51.

(2*S*)-3-Hydroxy-2-[*N*-phenylmethyl-(*N*-methoxycarbonylamino)amino]propanoic Acid (168)

The literature procedure[54] for generation of analogous compounds was followed with the modifications outlined below. Compound **167** (5.14 g, 14.9 mmol), **155** (2.62 g, 14.6 mmol), and dichloromethane (35 mL) were stirred at 0 °C for 1 h. Sodium phosphate buffer (30 mL, pH 7) and H_2O (20 mL) were added. The aqueous phase was acidified with HCl (12 M) to bring the pH ≤ 2.2 and the mixture was extracted with EtOAc (2 X 30 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated *in vacuo* . The residue was recrystallized from EtOAc/hexanes to give a colourless solid (1.01 g, 3.76 mmol, 26 % yield): mp 123-123.5 °C; IR ($CHCl_3$ cast) 3280, 2990, 1722, 1248 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.40 (m, 5H, ArH), 4.23 (d, 1H, J=13.5 Hz, CHHPh), 4.14 (d, 1H, J=13.5 Hz, CHHPh), 3.93 (m, 1H, CHHCH), 3.81 (m, 1H, CHHCH), 3.75 (m, 1H, C$\underline{H}$), 3.61 (s, 3H, C$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.50 ($\underline{C}O_2H$), 158.49 ($\underline{C}O_2R$), 135.92 (Ar$\underline{C}$), 129.02 (Ar$\underline{C}$), 128.44 (Ar$\underline{C}$), 127.85 (Ar$\underline{C}$), 66.16 ($\underline{C}H_2O$), 61.45 ($\underline{C}H_3$), 59.50 ($\underline{C}H_2N$), 52.82 ($\underline{C}H$); exact mass 268.1051 (268.1059 calcd. for $C_{12}H_{16}N_2O_5$); Anal. Calcd. for $C_{12}H_{16}N_2O_5$: C, 53.73; H, 6.01; N, 10.44; Found: C, 53.52; H, 6.07; N, 10.27.

(2*S*)-3-Hydroxy-2-[(methoxycarbonylamino)amino]propanoic Acid (169)

The literature procedure[146] for generation of analogous compounds was adapted. To a solution of **168** (0.27 g, 1.0 mmol) in EtOH (10 mL) was added palladium chloride (0.02 g, 0.1 mmol) and the mixture was stirred under 1 atm of hydrogen for 4 h. The mixture was filtered through Celite and concentrated *in vacuo*. The residue was separated on an MPLC column twice (RP8, Merck Lobar, 10 % CH_3CN/H_2O) to give a colourless oil (100 mg, 0.56 mmol, 56 % yield): IR (neat film) 3320, 2990, 1740, 1710, 1520, 1280 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 3.78 (dd, 1H, J=4.4, 12.0 Hz, C$\underline{H}$H), 3.74 (s, 3H, C$\underline{H}_3$), 3.73 (dd, 1H, J=5.2, 12.0 Hz, CH$\underline{H}$), 3.62 (dd, 1H, J=4.4, 5.2 Hz, C$\underline{H}$); ^{13}C NMR (100 MHz, CD_3OD) δ 174.30 ($\underline{C}O_2H$), 160.26 ($\underline{C}O_2R$), 66.05 ($\underline{C}H_2O$), 61.70 (O$\underline{C}H_3$), 52.95 ($\underline{C}H$); exact mass 178.0590 (178.0589 calcd. for $C_5H_{10}N_2O_5$).

Benzyloxycarbonylbenzaldimine (171)[147]

The literature procedure[143] for generation of analogous compounds was adapted. Compound **161** (4.47 g, 25.2 mmol), $CHCl_3$ (20 mL) and benzyl chloroformate (3.6 mL, 4.3 g, 25. mmol) were stirred at 0 °C for 10 min, and then stirred at 20 °C for 18 h. The mixture was concentrated *in vacuo* and Vigreaux distilled (10 cm) to give a colourless oil (2.12 g, 8.87 mmol, 35 %): bp 156-168 °C, 0.6 torr; IR ($CHCl_3$ cast) 3400, 3040, 2262, 1720, 1210 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 9.0 (s, 1H, C$\underline{H}$), 7.3-8.3 (m, 10H, Ph$\underline{H}$), 5.5 (s, 2H, C$\underline{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.12 ($\underline{C}$=N), 163.62 ($\underline{C}$=O), 135.32 (ArC), 133.81 (ArC), 130.31 (ArC), 128.87 (ArC), 128.53 (ArC), 128.50 (ArC), 128.44 (ArC), 68.81 (CH$_2$); exact mass 239.0954 (239.0961 calcd. for $C_{15}H_{13}NO_2$).

Phenylmethoxycarbonylbenzamide (172)[147]

The literature procedure[54] for generation of analogous compounds was followed with the modifications outlined below. To a solution of **171** (47 mg, 0.20 mmol) in $CHCl_3$ (5 mL) and pyridine (0.9 mL, 0.9 mg, 10 mmol) was added oxone® (0.90 g, 1.5 mmol) and stirred for 62 h. The mixture was filtered and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 3:1) gave a colourless powder (38 mg, 0.15 mmol, 74 % yield): IR (CCl_4 cast) 1730, 1711 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (br. s, 1H, NH), 7.82 (d, 2H, J=8.0 Hz, ArH), 7.30-7.60 (m, 3H, ArH), 5.23 (s, 2H, CH$_2$); exact mass 255.0895 (255.0895 calcd. for $C_{15}H_{13}NO_3$).

N-[(2,2,2-Trichloroethoxy)carbonyl]benzaldimine (173)[147]

The literature procedure[143] for generation of analogous compounds was adapted. To a solution of **161** (2.05 g, 11.6 mmol) in dichloromethane (20 mL) at 0 °C was added 2,2,2-trichloroethyl chloroformate (2.75 g, 13.0 mmol) in dichloromethane (10 mL). After 3 h the mixture was concentrated *in vacuo*. The residue was bulb to bulb distilled twice. The resulting oil crystallized overnight to give a colourless solid (2.95 g, 10.5 mmol, 91 % yield): mp 45-46 °C; IR (CCl_4 cast) 2980, 1724, 1627, 1200, 1185 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H, CHN), 7.97 (d, 2H, J=7.9 Hz, ArH), 7.35-7.65 (m, 3H, ArH), 4.94 (s, 2H, CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.31 (C=N), 162.41 (CO_2N), 134.34 (ArC), 133.56 (ArC), 130.65 (ArC), 128.99 (ArC), 94.61 (CCl_3), 76.00 (CH_2); exact mass 245.9905 (245.9902 calcd. for $C_{10}H_8NO_2{}^{35}Cl^{37}Cl$, M^+-Cl).

(*RS*)-[(2,2,2-Trichloroethoxy)carbonylamino]phenylmethyl Alcohol (174)[147]

The literature procedure[54] for generation of analogous compounds was followed with the modifications outlined below. A suspension of **173** (120 mg, 0.43 mmol) in $CHCl_3$ (2 mL) and K_2CO_3 (1.0 g, 7.2 mmol) in H_2O (4 mL) at 0 °C, was stirred with oxone® (1.3 g, 2.11 mmol) in H_2O (6.5 mL) for 90 min. The layers were separated and the organic layer was washed with H_2O (7 mL) and concentrated *in vacuo*. Flash chromatography (CH_2Cl_2) gave an unstable colourless solid (39. mg, 0.15 mmol, 34 % yield): mp 137-140 °C; IR (CH_2Cl_2 cast) 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.60 (m, 5H, Ar$\underline{H}$), 6.16 (d, 1H, J=8.8 Hz, C$\underline{H}$), 5.91 (d, 1H, J=8.0 Hz, O$\underline{H}$), 4.70-4.90 (m, 3H, N$\underline{H}$ & C$\underline{H}_2$); exact mass 296.9718 (296.9726 calcd. for $C_{10}H_{10}NO_3{}^{35}Cl_3$).

[(2,2,2-Trichloroethoxy)carbonyl]benzamide (175)[147]

The literature procedure[101] for generation of analogous compounds was followed with the modifications outlined below. To a solution of **173** (0.12 g, 0.43 mmol) in dichloromethane (7 mL) at 0 °C was added *m*-chloroperbenzoic acid (0.17 g, 0.99 mmol) in dichloromethane (2 mL) during 5 min. After 1 h, the mixture was washed with $NaHCO_3$ (4 X 10 mL), H_2O (3 X 30 mL) and dried with $CaCl_2$. Flash chromatography (hexanes:EtOAc 3:1) gave **175** as a colourless powder (72 mg, 0.24 mmol, 56 % yield): mp 119-121 °C; IR (CH_2Cl_2 cast) 3230, 1764, 1691, 1530, 1200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.76 (br. s, 1H, N$\underline{H}$), 7.90 (d, 2H, J=8.0 Hz, Ar$\underline{H}$), 7.45-7.65 (m, 3H, Ar$\underline{H}$), 4.83 (s, 2H, C$\underline{H}_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.91 ($\underline{C}$ON), 149.34 ($\underline{C}O_2N$), 133.37 (Ar$\underline{C}$), 132.48 (Ar$\underline{C}$), 128.93 (Ar$\underline{C}$), 127.91 (Ar$\underline{C}$), 94.46 ($\underline{C}Cl_3$), 74.79 ($\underline{C}H_2$); exact mass 294.9553 (294.9569 calcd. for $C_{10}H_8NO_3{}^{35}Cl_3$).

2-(Trimethylsilyl)ethyl Chloroformate (176)[147]

A solution of 2-(trimethylsilyl)ethanol (2.15 mL, 1.77 g, 15.0 mmol) in $PhCH_3$ (5 mL) was added to phosgene (3 mL, 4 g, 40 mmol) and the mixture was stirred overnight. Ar was blown through the solution for 4 h and the solution was concentrated *in vacuo*. The residue was distilled to give a colourless oil (1.19 g, 6.58 mmol, 44 % yield): bp 77-78 °C, 80 torr; IR (neat film) 2957, 1778, 1253, 1147 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (m, 2H, $C\underline{H}_2O$), 1.11 (m, 2H, $C\underline{H}_2Si$), 0.50 (s, 9H, $(C\underline{H}_3)_3$); ^{13}C NMR (MHz, 100 MHz) δ 150.5 ($\underline{C}$=O), 71.3 ($\underline{C}H_2O$), 17.5 ($\underline{C}H_2Si$), 1.0 ($\underline{C}H_3$); exact mass 73.0496 (73.0473 calcd. for C_3H_9Si); Anal. Calcd. for $C_6H_{13}ClO_2Si$: C, 39.86; H, 7.25; Found: C, 40.23; H, 7.65.

2-(Trimethylsilyl)ethoxycarbonylbenzaldimine (178)[147]

The literature procedure[143] for generation of analogous compounds was adapted. To a solution of **161** (1.26 g, 7.11 mmol) in dichloromethane (5 mL) at 0 °C was added **176** (1.0 g, 5.5 mmol) in dichloromethane (5 mL) and the mixture was stirred for 20 h. The mixture was concentrated *in vacuo*, and the residue was bulb to bulb distilled to give an oil (1.09 g, 4.37 mmol, 79 % yield): bp 145-180 °C, 0.4 torr; IR (film) 2990, 1715, 1632, 1225, 1200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H, $C\underline{H}$), 7.88 (d, 2H, J=7.9 Hz, $Ar\underline{H}$), 7.40-7.55 (m, 3H, $Ar\underline{H}$), 4.33 (m, 2H, $C\underline{H}_2O$), 1.11 (m, 2H, $C\underline{H}_2Si$), 0.30 (s, 9H, $(C\underline{H}_3)$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.37 ($\underline{C}$=N), 163.75 (C=O), 133.58 ($Ar\underline{C}$), 130.15 ($Ar\underline{C}$), 128.78 ($Ar\underline{C}$), 65.38 ($\underline{C}H_2O$), 17.37 ($\underline{C}H_2Si$), -1.65 ($(\underline{C}H_3)_3$); exact mass 248.1107 (248.1107 calcd. for $C_{13}H_{18}NO_2Si$; Anal. Calcd. for $C_{13}H_{18}NO_2Si$: C, 62.61; H, 7.68; N, 5.62; Found: C, 62.98; H, 7.56; N, 5.78.

Benzyl (*R*)-3-*O*-Benzylglycerate[108] (181)

The literature procedure was modified: To a solution of **188** (1.48 g, 7.55 mmol) in dimethyl formamide (10 mL) and Me_4NOH pentahydrate (1.26 g, 6.95 mmol) at 20 °C was added benzyl bromide (0.83 mL, 1.2 g, 7.0 mmol), and the mixture was stirred for 21 h. H_2O (15 mL) was added, and the mixture was extracted with Et_2O (3 X 25 mL). The organic layer was dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 4:1) gave the known **181** as a colourless oil (1.91 g, 6.72 mmol, 96 % yield): IR ($CHCl_3$ cast) 3430, 2664, 1749, 1125 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.20-7.41 (m, 10H, ArH), 5.24 (d, 1H, J=12.3 Hz, CHHPh ester), 5.20 (d, 1H, J=12.3 Hz, CHHPh ester), 4.56 (d, 1H, J=12.1 Hz, CHHPh ether), 4.48 (d, 1H, J=12.2 Hz, CHHPh ether), 4.35 (m, 1H, CH), 3.78 (dd, 1H, J=3.5, 10.5 Hz, CHHCH), 3.74 (dd, 1H, J=3.0, 9.8 Hz, CHHCH), 3.13 (d, 1H, J=7.0 Hz, OH); exact mass 195.0662 (195.0654 calcd. for $C_{10}H_{11}O_4$); MS (CI, NH_3) 304 (MNH_4^+); Anal. Calcd. for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.28; H, 6.28.

Benzyl (*S*)-3-Benzyloxy-2-[(*t*-butyloxycarbonylamino)amino]propanoate (182)

The literature procedure[107] for generation of analogous compounds was modified. Trifluoromethanesulfonic anhydride (0.63 mL, 1.1 g, 3.7 mmol), was added to **181** (1.05 g, 3.37 mmol), in dichloromethane (8 mL) at -78 °C. After 6 min 2,6-lutidine (0.45 mL, 0.41 g, 3.9 mmol) was added. After another 6 min *t*-butylcarbazate (**76**) (0.89 g, 6.7 mmol) and another portion of 2,6-lutidine (0.45 mL, 0.41 g, 3.9 mmol) were added. After 30 min, the mixture was warmed to 20 °C and concentrated *in vacuo*. Flash chromatography (hexanes:EtOAc 1:1) gave the known **182** as a colourless oil (0.69 g, 1.7 mmol, 51 % yield): IR ($CHCl_3$ cast) 3420, 2995, 1740, 1719, 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.35 (m, 10H, ArH), 6.41 (br. s, 1H, NH), 5.22 (d, 1H, J=12.0 Hz, CHHPh ester), 5.13 (d, 1H, J=12.0 Hz, CHHPh ester), 4.54 (d, 1H, J=14.0 Hz,

$\mathrm{C\underline{H}HPh}$ ether), 4.42 (d, 1H, J=14.0 Hz, $\mathrm{CH\underline{H}Ph}$ ether), 3.90 (br. s, 1H, $\mathrm{C\underline{H}}$), 3.78 (br. s, 2H, $\mathrm{C\underline{H}_2CH}$), 1.42 (s, 9H, $\mathrm{(C\underline{H}_3)_3}$); exact mass 400.2005 (400.1998 calcd. for $C_{22}H_{28}N_2O_5$); Anal. Calcd. for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 6.99. Found: C, 66.09; H, 7.14; N, 7.16.

D-(+)-Galactose Diacetonide (189)

The literature procedure[100] was followed using the amounts outlined below. Galactose **180** (100. g, 555 mmol) in acetone (8.0 L, 110 mol) was stirred with sulfuric acid (80. mL, 1.4 mol) at 20 °C for 4 h. A stream of ammonia gas was blown through the solution for 5 min, the NH_4SO_4 was filtered, and the filtrate was concentrated *in vacuo*. The residue was distilled to give the known **189** as an oil (130. g, 473 mmol, 85 % yield): bp 120-125 °C, 0.1 torr (lit[100] bp 110-120, 0.1-0.2 torr); IR ($CHCl_3$ cast) 3480, 3000, 1070 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.58 (d, 1H, J=5.0 Hz, C-1$\underline{H}$), 4.62 (dd, 1H, J=3.0, 8.0 Hz, C-3$\underline{H}$), 4.34 (dd, 1H, J=3.0, 5.0, C-2$\underline{H}$), 4.28 (dd, 1H, J=2.0, 8.0 Hz, C-4$\underline{H}$), 3.95-3.67 (m, 3H, C-5$\underline{H}$ & C-6$\underline{H}$), 1.54 (s, 3H, $\mathrm{C\underline{H}_3}$), 1.46 (s, 3H, $\mathrm{C\underline{H}_3}$), 1.34 (s, 6H, 2 X $\mathrm{C\underline{H}_3}$); exact mass 245.1025 (245.1025 calcd. for $C_{11}H_{17}O_6$).

6-*O*-Benzylgalactose Diacetonide (190)

The literature procedure[100] was followed using the amounts outlined below. Compound **189** (113.7 g, 437.4 mmol) in $PhCH_3$ (110 mL) and benzyl chloride (103 mL, 113 g, 893 mmol) was heated to reflux with potassium hydroxide (155 g, 2.77 mmol) for 5 h. Ice water (250 mL) was added, the organic layer was washed with H_2O (3 X 250 mL), and the mixture was concentrated *in vacuo*. The residue was distilled to give the known **190** as an oil (146.9 g, 419.6 mmol, 96 % yield): bp 140 °C, 0.01 torr (lit[100] bp 130-160, 0.01 torr); IR (CH_2Cl_2 cast) 2988, 1454, 1381, 1211, 1070 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5H, Ar$\underline{H}$), 5.55 (d, 1H, J=3.0 Hz, C-1$\underline{H}$), 4.50-4.68 (m, 3H, C-3$\underline{H}$ & $\mathrm{C\underline{H}_2Ph}$), 4.24-4.35 (m, 2H, C-4$\underline{H}$ & C-2$\underline{H}$), 4.02 (ddd, 1H, J=2.0, 2.0, 4.0 Hz, C-5$\underline{H}$), 3.60-3.75 (m, 2H, C-6H$_2$), 1.55 (s, 3H, CH$_3$), 1.44 (s, 3H, CH$_3$), 1.34 (s, 6H, (CH$_3$)$_2$); exact mass 350.1742 (350.1729 calcd. for $C_{19}H_{26}O_6$); Anal. Calcd. for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.81; H, 7.59.

Methyl 6-*O*-Benzylgalactoside (191)

The literature procedure[100] was followed using the amounts outlined below. Compound **190** (18.4 g, 52.6 mmol) and 51.1 g of a 2.1 % methanolic HCl solution (1.07 g, 29.3 mmol) were heated to reflux for 3 h. The mixture was cooled and stirred with silver oxide (4.60 g, 19.8 mmol) for 3.5 h. The mixture was filtered through Celite and a stream of hydrogen sulfide was bubbled through the filtrate for 10 min. The mixture was filtered through Celite again and the filtrate was concentrated *in vacuo*. The resulting oil was crystallized twice from boiling EtOH (20 mL) to give the known **191** as colourless crystals (2.91 g, 10.7 mmol, 20 % yield): mp 140-142 °C (lit[100] mp 144-145 °C); IR ($CHCl_3$ cast) 3240, 2860, 1454, 1042 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30-7.40 (m, 5H, ArH), 4.84 (d, 1H, J=4.0 Hz, C-1H), 4.60 (s, 2H, CH$_2$Ph), 3.75-4.08 (m, 6H, C-2H, C-3H, C-4H, C-5H & C-6H), 3.44 (s, 3H, CH$_3$), 3.08 (br. s, 1H, OH), 2.87 (br. s, 1H, OH), 2.28 (br. d, 1H, J=8.0 Hz, OH); exact mass 284.1257 (284.1260 calcd. for $C_{14}H_{20}O_6$); Anal. Calcd. for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.76; H, 7.33.

(*R*)-3-*O*-Benzylglyceric Acid (188)

The literature procedure[100, 106] was followed using the amounts outlined below. Sodium meta-periodate (40.0 g, 187 mmol) was dissolved in warm (40 °C) H_2O (300 mL) and the solution was cooled to 0 °C. Compound **191** (20.0 g, 73.5 mmol) was added, and the reaction mixture was stirred at 20 °C for 19 h. Et_2O (400 mL) was added, the layers were separated, and the aqueous phase was filtered. The aqueous phase was further extracted with Et_2O (3 X 400mL), and the organic layers were pooled. H_2O (100 mL) was added to the organic phases and the mixture was concentrated *in vacuo* until all the Et_2O was removed. H_2O (250 mL) and a solution of potassium iodide (69.9 g, 0.421 mmol) and iodine (55.9 g, 0.220 mmol) in H_2O (90 mL) were added. After 10 min a buffered solution containing K_2CO_3 (65.7 g, 0.475 mmol) and $KHCO_3$ (48.7 g, 0.486 mmol) in H_2O (500 mL) was added and the resulting mixture was stirred in the dark for 2 h at 20 °C. H_2SO_4 (10 M, 142 mL, 1.42 mol) and sodium thiosulfate (40.2 g, 0.254 mmol) were added and the mixture was extracted with Et_2O (4 X 1L). H_2O (100 mL) was added and the mixture was concentrated *in vacuo* until only the water remained. The mixture was heated on the steam bath for 3.5 h, filtered, and extracted with Et_2O (4 X 100 mL). The organic phase was dried on Na_2SO_4, filtered, and concentrated *in vacuo* to give the known **188** as a syrup (13.7 g, 70.1 mmol, 95 % yield): IR ($CHCl_3$ cast) 3240, 3120, 2870, 1738, 1124 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.20-7.40 (m, 5H, Ar$\underline{H}$), 4.60 (s, 2H, $C\underline{H_2}Ph$), 4.38 (t, 1H, J=4.0 Hz, $C\underline{H}$), 3.80 (dd, 2H, J=1.8, 4.0 Hz, $C\underline{H_2}CH$); exact mass 196.0734 (196.0732 calcd. for $C_{10}H_{12}O_4$); Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.31; H, 6.40.

(2*S*)-2-[(*t*-Butyloxycarbonylamino)amino]-3-hydroxypropanoic Acid (193)

The literature procedure[146] for generation of analogous compounds was adapted. To a solution of **182** (0.51 g, 1.3 mmol) in CH_3OH (10 mL) was added 3 % $Pd(OH)_2$ on carbon (0.51 g, 110 μmol), and the mixture was stirred at 20 °C under hydrogen atmosphere until uptake ceased. The mixture was filtered through a bed of Celite and concentrated *in vacuo* to give crude **193** as an unstable colourless oil (0.34 g, 1.6 mmol, 120 % mass balance). The oil had the following spectral characteristics: IR ($CHCl_3$ cast) 3200, 2980, 1705, 1588, 1163 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3/CD_3OD$) δ 3.38 (m, 3H, $C\underline{H}C\underline{H_2}$), 1.50 (s, 9H, $(C\underline{H_3})_3C$); exact mass 164.0431 (164.0433 calcd. for $C_4H_8N_2O_5$).

Benzyl (*S*)-3-Benzyloxy-2-[amino(amino)]propanoate Hydrochloride (194)

The literature procedure[141] for generation of analogous compounds was adapted. TFA (3.5 mL, 5.2 g, 45. mmol) was added to **182** (137. mg, 0.342 mmol) and stirred for 30 min at 20 °C. The mixture was concentrated *in vacuo* and the residue was redissolved in 1M HCl (4 mL, then 2 X 1 mL with concentration between each addition). The resulting residue was recrystallized from 95 % EtOH (50.1 mg, 134 µmol, 39 % yield): mp 134-135 °C; IR (CH_3OH cast) 2920, 1735, 1210 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 7.20-7.40 (m, 10H, ArH), 5.29 (d, 1H, J=4.7 Hz, CHHPh ester), 5.18 (d, 1H, J=4.7 Hz, CHHPh ester), 4.52 (d, 1H, J=4.7 Hz, CHHPh ether), 4.40 (d, 1H, J=4.7 Hz, CHHPh ether), 4.00 (dd, 1H, J=1.0, 1.5 Hz, CHN), 3.92 (dd, 1H, J=1.5, 3.8 Hz, CHHCH), 3.82 (dd, 1H, J=1.0, 3.8 Hz, CHHCH); ^{13}C NMR (75 MHz, CD_3OD) δ 171.48 (CO), 138.62 (ArC), 136.68 (ArC), 129.59 (ArC), 129.50 (ArC), 129.41 (ArC), 128.90 (ArC), 74.42 (CH_2Ph ether), 69.98 (CH_2CH), 68.51 (CH_2Ph ester), 61.96 (CH); exact mass 300.1474 (300.1472 calcd. for $C_{17}H_{20}N_2O_3$); Anal. Calcd. for $C_{17}H_{21}ClN_2O_3$: C, 60.62; H, 6.28; N, 8.32. Found: C, 60.41; H, 6.36; N, 8.15.

Stereochemical Analysis of (*RS*)-Serine (196) via Reaction with Marfey's Reagent (195): (*S*)-Serine-2,4-dinitrophenyl-(*S*)-alaninamide (197), (*R*)-Serine-2,4-dinitrophenyl-(*S*)-alaninamide (198)

The literature procedure[110, 148] was followed using the amounts outlined below. (*RS*)-Serine (**196**) (30.0 µL, 77.9 µmol/mL, 2.30 µmol) in H_2O, N_α-(2,4-dinitro-5-fluorophenyl)-(*S*)-alaninamide (**195**) (100 µL, 31.7 nmol/µL, 3.20 µmol) in acetone and $NaHCO_3$ (20.0 µL, 1.0M, 20.0 µmol) in H_2O were stirred together at 37 °C for 1 h. After the mixture was cooled to 20 °C, HCl (10.0 µL, 2.0M, 20.0 µmol) was added and the mixture was centrifuged under vacuum to dryness. DMSO (0.5 mL) was added, 100. µL of this solution was diluted with H_2O (100. µL) and analysed by HPLC using 5.0 µL injections. Biorad HPLC, UV monitor model 1305A Gradient Module, Waters Radial

Compression Module (RP18, flow=1.5 mL/min, 10 % CH_3CN/TEAP buffer (pH 3.0) linear gradient over 45 min to 50 % CH_3CN/TEAP buffer (pH 3.0), detected by UV absorbance at 340 nm. Compound **197** t_R=17.92 min (*S*,*S* isomer) 50 %, **198** t_R=18.89±0.02 min (*R*,*S* isomer) 50 %. The isolated products were analyzed with a Hewlett-Packard 8452A UV-vis diode array spectrophotometer: Compound **197**: λ_{MAX}=338, 412 nm, **198**: λ_{MAX}=338, 412 nm. Further HPLC analysis using the Hewlett Packard 1082B, same column but 35 % B (24 % CH_3CN/TEAP buffer pH 3.0), showed **197** t_R=6.65 min (*S*,*S* isomer), λ_{MAX}=335 nm, **198** t_R=7.20 min (*R*,*S* isomer).

Stereochemical Analysis of Hydrazinoserine (151) via Reduction and Reaction with Marfey's Reagent 195: (*S*)-Serine-2,4-dinitrophenyl-(*S*)-alaninamide (200)

The literature procedure[110, 114] for generation of analogous compounds was adapted. Hydrazinoserine (**151**) (3.5 mg, 22 μmol) in H_2O (0.5 mL) and acetic acid (1 drop) was stirred with platinum oxide (0.2 mg, 1 μmol) under an hydrogen atmosphere at 20 °C for 1 day. The mixture was filtered through Celite and lyophilized. The residue was dissolved in H_2O (1 mL) and this (50.0 μL, 2.75 μmol) was treated with N_α-(2,4-dinitro-5-fluorophenyl)-(*S*)-alaninamide (**195**) (120 μL, 31.7 nmol/μL, 3.80 μmol) in acetone and $NaHCO_3$ (20.0 μL, 1.0M, 20.0 μmol) in H_2O and the mixture was stirred at 37 °C for 1 h. After the mixture was cooled to 20 °C, HCl (10.0 μL, 2.0M, 20.0 μmol) was added and the mixture was centrifuged under vacuum to dryness. DMSO (0.5 mL) was added, 100. μL of this solution was diluted with H_2O (100. μL) and this solution (A) was analyzed by HPLC: **197** t_R=17.98 min (*S*,*S* isomer) 99 %, **198** t_R=18.93 min (*R*,*S* isomer) 1 %. Further HPLC analysis of solution (A) using the Hewlett Packard 1082B, same column but 35 % B (24 % CH_3CN/TEAP buffer pH 3.0), showed the following retention time **200** t_R=6.67 min (*S*,*S* isomer) λ_{MAX}=335 nm. A coinjection of the solution (A) (80 μL) with

197 and **198** (5 µL) showed **197** t_R=6.77 min (*S*,*S* isomer), and **198** t_R=7.26 min (*R*,*S* isomer).

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APPENDIX

X-RAY CRYSTAL STRUCTURE DATA FOR 125.

A pale yellow prism of $C_{22.75}H_{25}N_3O_5S$, with the approximate dimensions of 0.20 x 0.10 x 0.10 mm, was mounted on a glass fibre with epoxy, and optically centered in the x-ray beam of a Siemens P4RA automated diffractometer. All intensity measurements were performed using CuKα radiation (λ = 1.54178 Å) with an incident-beam graphite crystal monochromator.

The automatic peak search and reflection indexing programs generated a monoclinic cell. The systematic absences (hkl, h+k odd) were consistent with the space groups C2, Cm and C2/m; the space group C2 (No. 5) was confirmed by the successful solution and refinement of the structure.

The intensity data were collected with Wyckoff ($\omega/2\Theta$) scans at 29.30-6.01°/min (in ω), using ω scan width of 1.00°.

Peak backgrounds were measured with the crystal and detector stationary, at the beginning and end of each scan; this gave a peak-to-background counting time ratio of 1:1. Intensity measurements were made within the range $3.0^\circ < \Theta < 115^\circ$; A total of 7599 reflections were collected.

STRUCTURE SOLUTION AND REFINEMENT.

The structure was solved using the direct methods program SHELXTL PLUS. Adjustment of the atomic parameters of the non-hydrogen atoms was carried out by full-matrix least-squares refinement of F_o minimizing the function $\Sigma\omega(|F_o|-|F_c|)^2$ where $|F_o|$ and $|F_c|$ are the observed and calculated structure factor amplitudes and the weight ω is $(\sigma^2(F_o) + 0.0008F_o^2)^{-1}$.

The hydrogen atoms were generated at idealized calculated positions by assuming a C-H bond length of 0.96 Å and the appropriate sp^2 or sp^3 geometry. All hydrogen atoms were then included in the calculations with fixed isotropic gaussian displacement parameters and were constrained to 'ride' on the attached atoms.

Refinement of coordinates and isotropic U's for all non-hydrogen atoms was continued to convergence. At that stage, the data were corrected for absorption through use of a semi-empirical scheme; the maximum and minimum correction factors applied to F_o were 0.9157 and 0.7773. After averaging over 2 symmetry there were 6061 averaged reflections, 4266 with $F_o > 6\sigma(F_o)$. In the final cycle, 547 parameters were refined using the 4266 observations having $F_o > 6\sigma(F_o)$. The final goodness-of-fit was 1.76, and

$$R_1 = \Sigma \left| |F_o| - |F_c| \right| / \Sigma |F_o| = 0.0666$$

$$R_2 = (\Sigma\, \omega(|F_o| - |F_c|)^2 / \Sigma\, \omega F_o^2)^{1/2} = 0.0807$$

The largest positive and negative peaks in the final difference Fourier map had densities of 0.70 and -1.43 eÅ^{-3}, respectively.

TABLE: Experimental Details.

A. Crystal Data

$C_{22.75}H_{25}N_3O_5S$ F.W. 452.5

Crystal dimensions: 0.10 x 0.20 x 0.10 mm

monoclinic space group $C2$

a = 43.149(11), b = 7.582(2), c = 14.278(4) Å

β = 102.58(2)°

V = 4559.32 Å^3; Z = 8; D_c = 1.318 g cm^{-3}; μ = 1.592 mm^{-1}

B. Data Collection and Refinement Conditions

Diffractometer used: Siemens P4RA

Radiation: CuKα (λ = 1.54178 Å); graphite monochromator

Scan type: Wyckoff

Scan rate: 29.30-6.01°min^{-1} (in ω)

Scan width (ω): 1.00°

Data collection range: $3.0° \leq 2\Theta \leq 115.0°$

Data collection index range: ±h ±k ±l

Number of reflections: 6061 total, averaged; 4266

Observations: variables ratio: 4266: 547

Agreement factors R_1,R_2, GOF: 0.0666, 0.0807, 1.76

Corrections applied: absorption correction

STRUCTURE DETERMINATION SUMMARY

Crystal Data

Empirical Formula	$C_{22.75} H_{25} N_3 O_5 S$
Color; Habit	Pale yellow prisms
Crystal Size (mm)	0.10 x 0.20 x 0.10
Crystal System	Monoclinic
Space Group	C2
Unit Cell Dimensions	a = 43.149(11) Å
	b = 7.582(2) Å
	c = 14.278(4) Å
	β = 102.58(2)°
Volume	4559.320(0) $Å^3$
Z	8
Formula Weight	452.5
Density(calc.)	1.318 Mg/m^3
Absorption Coefficient	1.592 mm^{-1}
F(000)	1908

Data Collection

Diffractometer Used	Siemens P4RA
Radiation	CuKα ($\lambda = 1.54178$ Å)
Temperature (K)	295
Monochromator	Highly oriented graphite crystal
2θ Range	3.0 to 115.0°
Scan Type	Wyckoff
Scan Speed	Variable; 6.01 to 29.30°/min. in ω
Scan Range (ω)	1.00°
Background Measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 50.0% of total scan time
Standard Reflections	0 measured every 50 reflections
Index Ranges	$-46 \le h \le 46$, $-8 \le k \le 8$ $-15 \le \ell \le 15$
Reflections Collected	7599
Independent Reflections	6061 ($R_{int} = 3.53\%$)
Observed Reflections	4266 ($F > 6.0\sigma(F)$)
Absorption Correction	Semi-empirical
Min./Max. Transmission	0.7773 / 0.9157

Solution and Refinement

System Used	Siemens SHELXTL PLUS (VMS)
Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\sum w(F_o - F_c)^2$
Absolute Structure	$\eta = 1.11(6)$
Extinction Correction	$\chi = 0.00023(9)$, where $F^* = F\, [\, 1 + 0.002\chi F^2/\sin(2\theta)\,]^{-1/4}$
Hydrogen Atoms	Riding model, fixed isotropic U
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0008F^2$
Number of Parameters Refined	547
Final R Indices (obs. data)	R = 6.66 %, wR = 8.07 %
R Indices (all data)	R = 8.90 %, wR = 8.79 %
Goodness-of-Fit	1.76
Largest and Mean Δ/σ	0.325, 0.012
Data-to-Parameter Ratio	7.8:1
Largest Difference Peak	0.70 eÅ^{-3}
Largest Difference Hole	-1.47 eÅ^{-3}

Table 2. Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Coefficients ($Å^2$ x 10^3)

	x	y	z	U(eq)
S(1)	10480(1)	7959	6095(1)	44(1)
O(1)	10155(1)	7827(8)	6156(3)	60(2)
O(2)	10709(1)	8096(9)	6983(3)	61(2)
N(1)	10570(1)	6220(8)	5461(4)	42(2)
C(2)	10614(2)	6731(10)	4498(5)	45(3)
C(3)	10706(2)	8673(10)	4548(6)	50(3)
C(4)	10539(2)	9576(11)	5253(6)	50(3)
C(5)	10871(3)	8426(15)	3056(8)	91(5)
C(6)	10611(2)	9324(12)	3491(6)	66(3)
C(7)	11076(2)	7412(13)	3899(8)	77(4)
C(8)	11074(2)	8652(13)	4761(8)	75(4)
C(9)	11217(3)	10481(16)	4665(9)	110(6)
C(10)	11250(2)	7969(18)	5719(8)	94(4)
C(11)	10889(2)	5803(13)	4133(7)	75(4)
C(12)	10477(2)	4524(11)	5598(6)	56(3)
O(12)	10426(2)	3461(7)	4969(4)	74(2)
C(13)	10457(3)	4143(11)	6644(6)	66(4)
C(14)	10175(2)	3320(16)	6866(7)	88(4)
N(13)	10452(2)	2227(9)	6850(5)	54(3)
N(14)	10644(2)	1900(8)	7781(4)	46(2)
C(15)	10973(2)	1821(11)	7897(6)	57(3)
O(15)	11115(2)	2260(9)	7304(4)	81(3)
C(16)	11094(2)	1065(12)	8882(6)	55(3)
C(17)	10830(2)	658(10)	9254(6)	50(3)
C(18)	10540(2)	1065(11)	8541(6)	58(4)
O(18)	10267(2)	792(9)	8551(5)	80(3)
C(19)	10878(3)	-5(13)	10178(7)	72(4)
C(20)	11185(3)	-284(13)	10688(7)	77(4)
C(21)	11445(3)	133(14)	10307(7)	73(4)
C(22)	11395(3)	794(13)	9399(7)	69(4)
S(31)	7960(1)	-1789(4)	-3203(1)	53(1)
O(31)	8076(1)	-2095(10)	-4062(4)	77(2)
O(32)	8190(1)	-1690(9)	-2333(4)	76(2)
N(31)	7737(1)	70(9)	-3336(5)	51(3)
C(32)	7391(2)	-349(11)	-3648(6)	53(3)
C(33)	7348(2)	-2105(14)	-3180(5)	61(3)

Table 2 continued.

C(34)	7641(2)	-3227(11)	-3159(6)	60(3)
C(35)	7034(2)	-2843(15)	-3735(7)	85(4)
C(36)	6789(2)	-1587(22)	-3471(9)	125(6)
C(37)	7000(3)	-319(22)	-2740(9)	121(7)
C(38)	7261(2)	-1577(20)	-2219(7)	97(5)
C(39)	7147(3)	-3080(23)	-1704(9)	171(10)
C(40)	7523(3)	-671(21)	-1450(7)	125(7)
C(41)	7175(2)	942(17)	-3257(8)	99(5)
C(42)	7852(2)	1679(13)	-3598(6)	60(4)
O(42)	7672(1)	2709(9)	-4080(4)	79(3)
C(43)	8184(2)	2108(12)	-3166(6)	61(4)
C(44)	8334(2)	3619(13)	-3597(7)	81(4)
N(43)	8208(2)	3948(9)	-2753(5)	56(3)
N(44)	8422(2)	4125(9)	-1852(5)	56(3)
C(45)	8288(3)	4619(13)	-1082(6)	66(4)
O(45)	8006(2)	4612(12)	-1099(5)	94(3)
C(46)	8553(3)	5054(12)	-287(6)	67(4)
C(47)	8831(2)	4867(13)	-613(6)	66(4)
C(48)	8751(2)	4267(14)	-1612(7)	71(4)
O(48)	8920(2)	3894(14)	-2140(5)	127(5)
C(49)	9121(3)	5256(16)	-12(8)	94(5)
C(50)	9114(3)	5955(17)	885(10)	98(6)
C(51)	8850(4)	6113(16)	1217(8)	98(5)
C(52)	8548(3)	5699(16)	624(8)	98(6)
C(1S)	9963(2)	4312(10)	10237(6)	60
C(2S)	9823	4193	9262	60
C(3S)	9786	5704	8691	60
C(4S)	9889	7334	9096	60
C(5S)	10028	7453	10071	60
C(6S)	10065	5942	10642	60
C(7S)	10148	5993	11743	60

* Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor